L'hépatite chronique C
la fin d'une maladie chronique et une belle histoire

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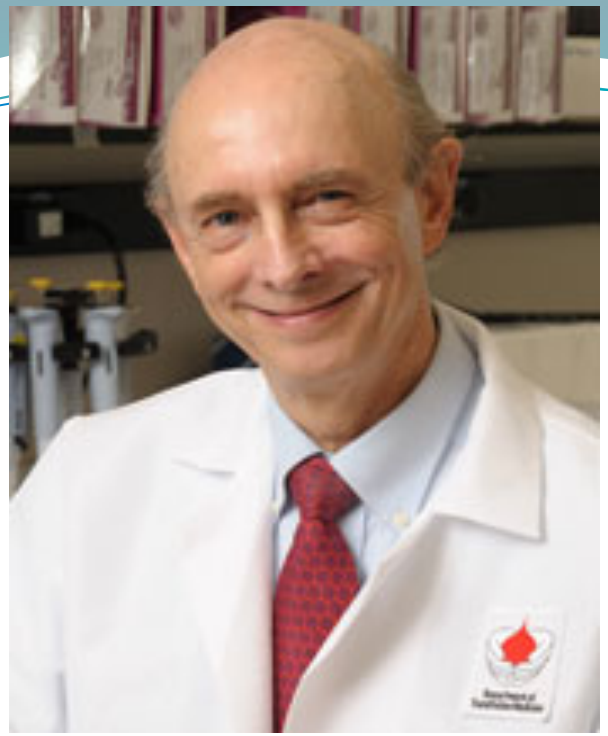
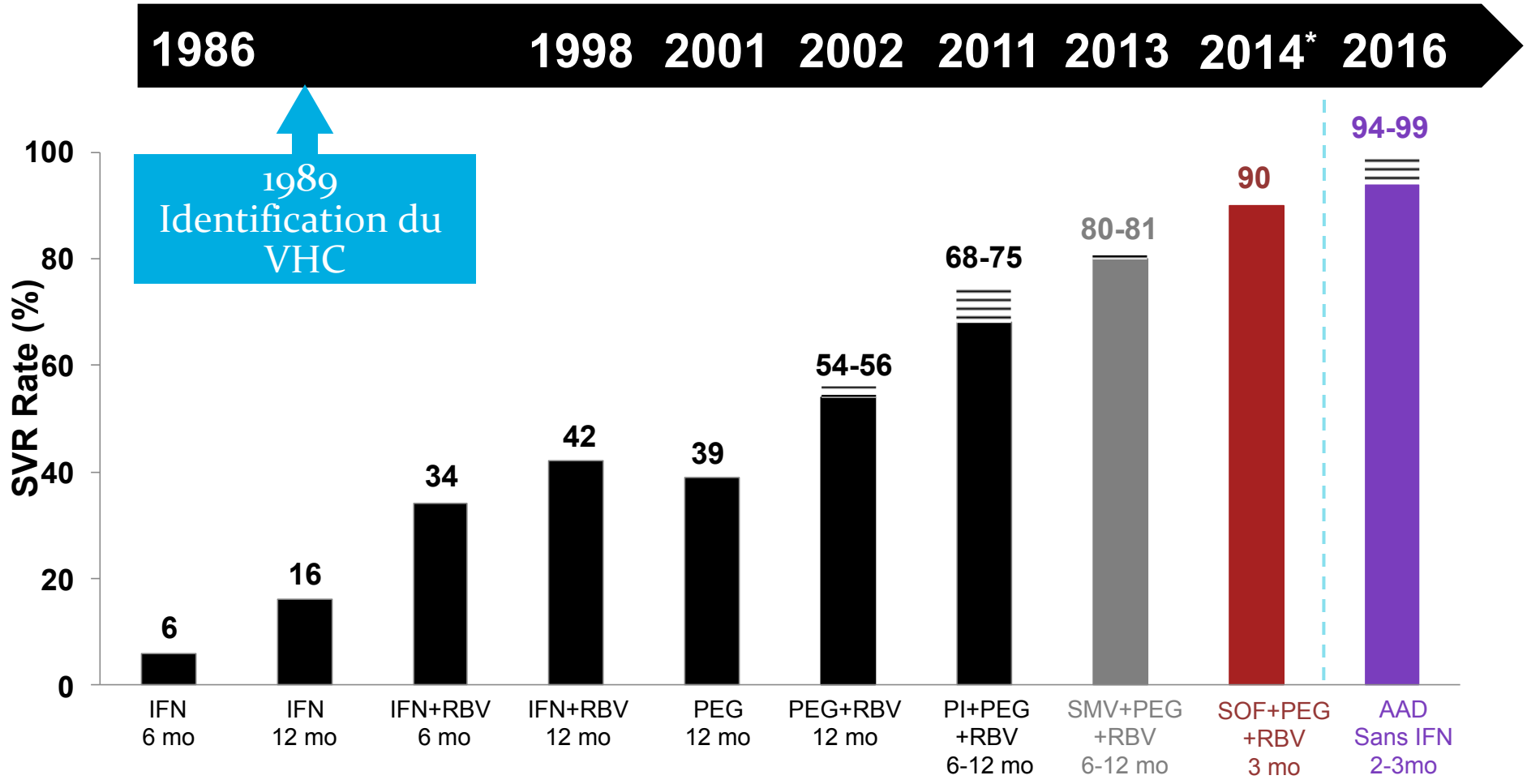


H Alter

M Houghton

J Hoofnagle

Quels progrès?



Year of data presentation at EASL 2014 and publication in *NEJM

Adapted from Strader DB, et al. Hepatology 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2013. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2014. Jacobson I, et al. EASL 2013. Amsterdam. The Netherlands. Poster #1425. Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413. Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02; Afdhal N, et al. *N Engl J Med* 2014; 370: 1889-98; Kowdley K, et al. *N Engl J Med* 2014; 370: 1879-88.

Tout a commencé avec: L'interféron alfa: 1986

ORIGINAL ARTICLE ARCHIVE

Treatment of Chronic Non-A, Non-B Hepatitis with Recombinant Human Alpha Interferon

Jay H. Hoofnagle, M.D., Kevin D. Mullen, M.D., D. Brian Jones, M.D., Vinod Rustgi, M.D., Adrian Di Bisceglie, M.D., Marion Peters, M.D., Jeanne G. Waggoner, B.A., Yoon Park, R.N., and E. Anthony Jones, M.D.

N Engl J Med 1986; 315:1575-1578 | December 18, 1986 | DOI: 10.1056/NEJM198612183152503

Share:

Abstract

We treated 10 patients who had chronic non-A, non-B hepatitis with recombinant human alpha interferon in varying doses (0.5 to 5 million units) daily, every other day, or three times weekly for up to 12 months.

In 8 of the 10 patients, elevated serum aminotransferase levels decreased rapidly during therapy and eventually fell into the normal or nearly normal range. In two of these patients, the interferon therapy was stopped after four months, and in both cases, a prompt return of aminotransferase activities to pretreatment values occurred. Prolonged treatment was associated with a sustained improvement in aminotransferase levels; in three cases, biopsy specimens obtained after one year of therapy showed marked improvement in hepatic histology, even though low doses of alpha interferon had been used.

These preliminary findings, although not adequately controlled, suggest that long-term, low-dose alpha interferon therapy may be effective in controlling the disease activity in some patients with chronic non-A, non-B hepatitis. A prospective controlled trial is now needed to assess the role of interferon therapy in this disease. (N Engl J Med 1986; 315:1575–8.)

MEDIA IN THIS ARTICLE

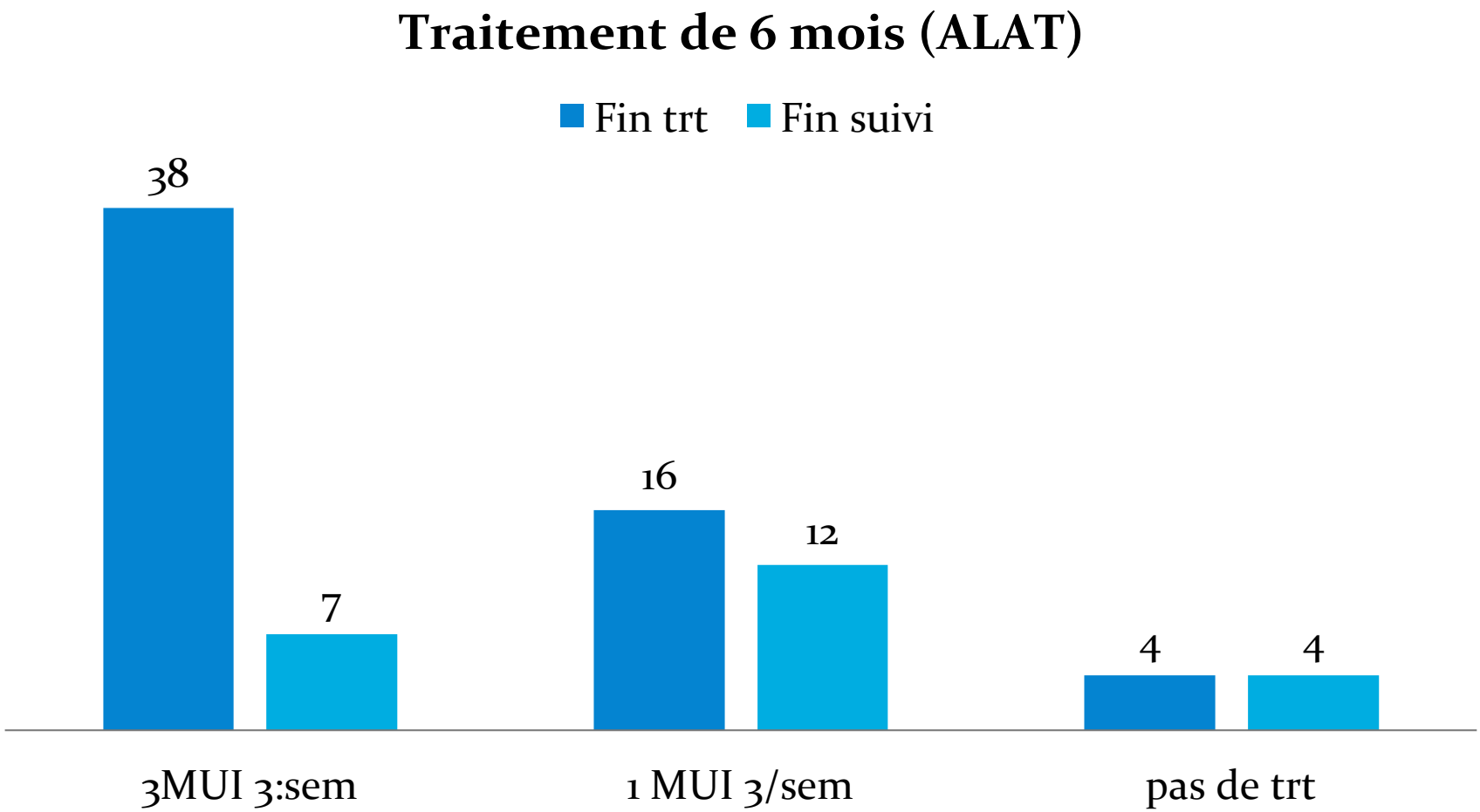
FIGURE 1

Serial Determinations of Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels in a Patient (No. 1) with Chronic Non-A, Non-B Hepatitis Who Was Treated for One Year with Daily Injections of Recombinant Human Alpha Interferon.

FIGURE 2

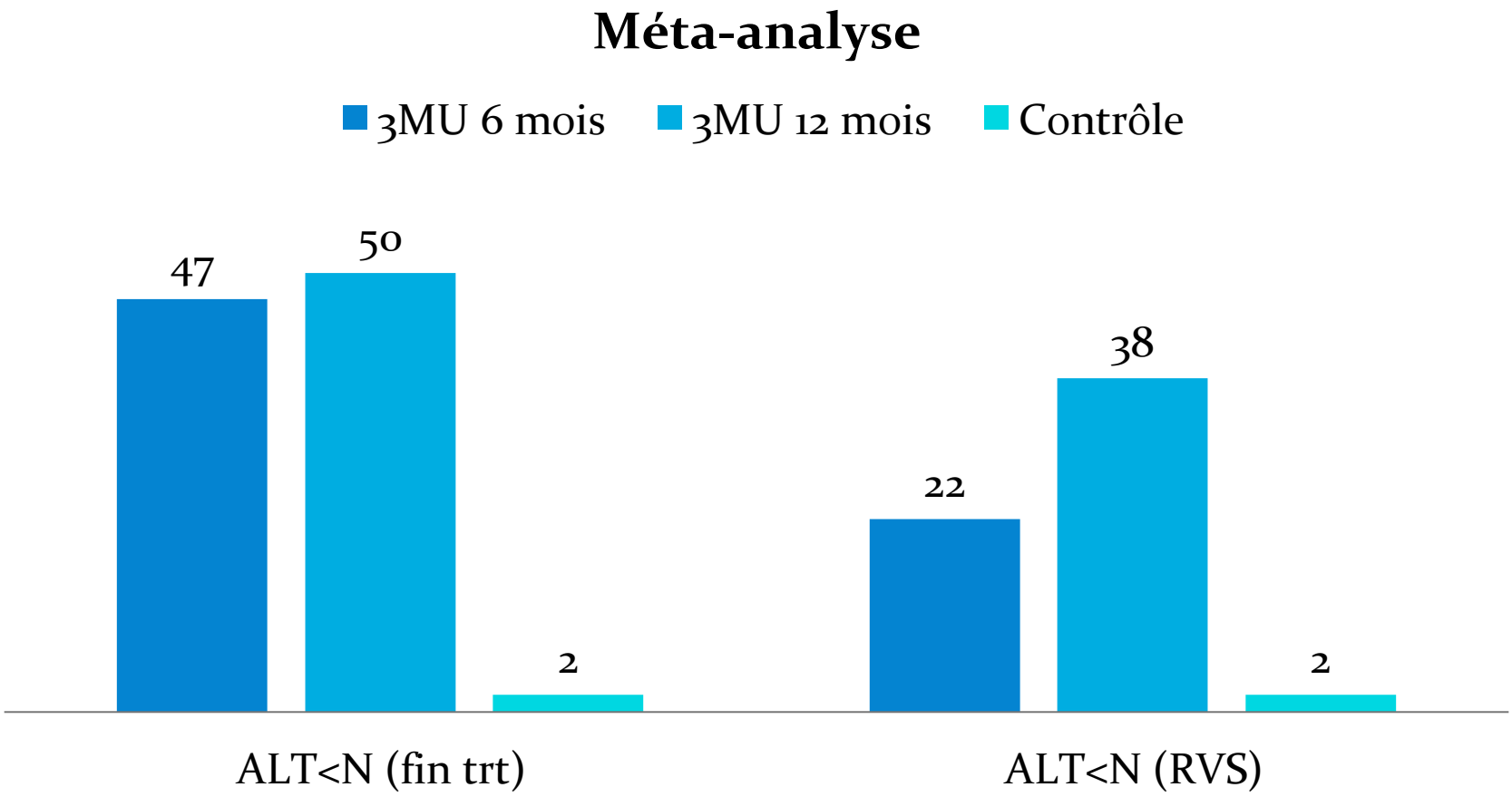
Serial Determinations of Alanine Aminotransferase (ALT) Levels in Two Patients (No. 3 and 4) with Chronic Non-A, Non-B Hepatitis Who Were Treated with Two Courses of Recombinant Human Alpha Interferon.

IFN a2b



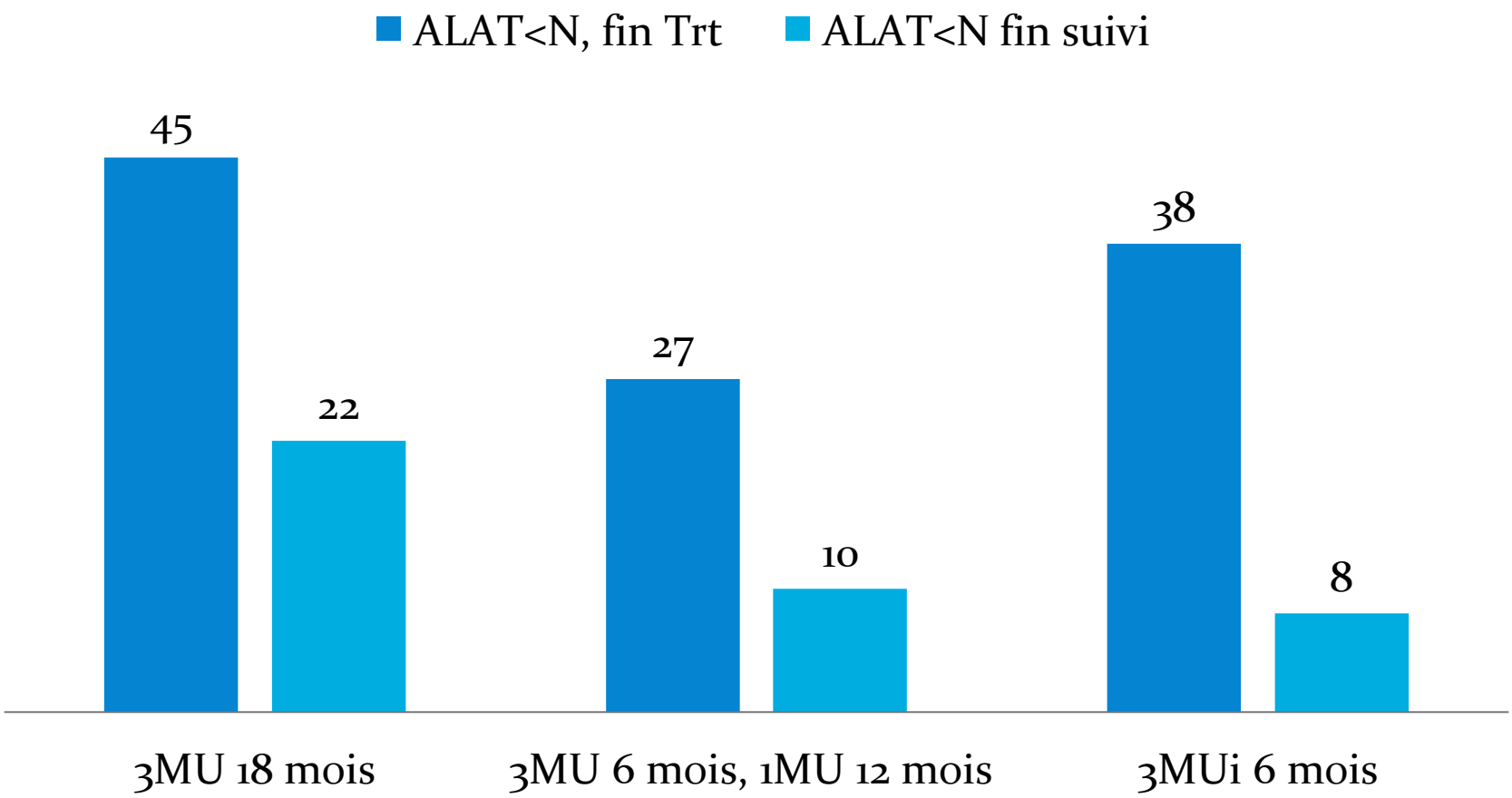
Davis et al, NEJM 1989

Interféron α



Poynard, Leroy et al Hepatology 1996

Interferon a2b: la bonne dose et la bonne durée?



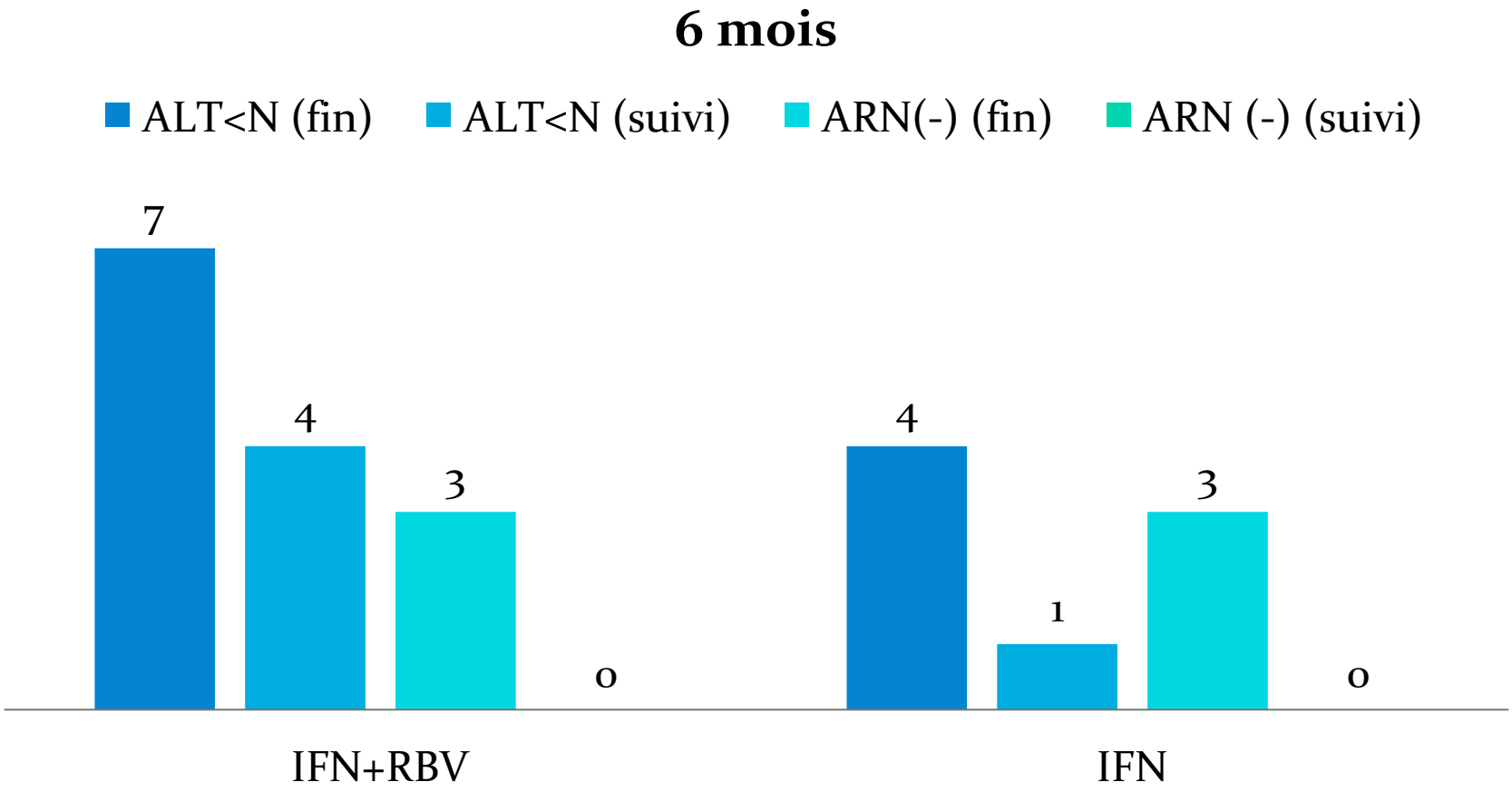
Poynard et al, NEJM 1995

Les années 1990:
la ribavirine et le génotype

Les années 1990

Chute du Mur de Berlin 1989

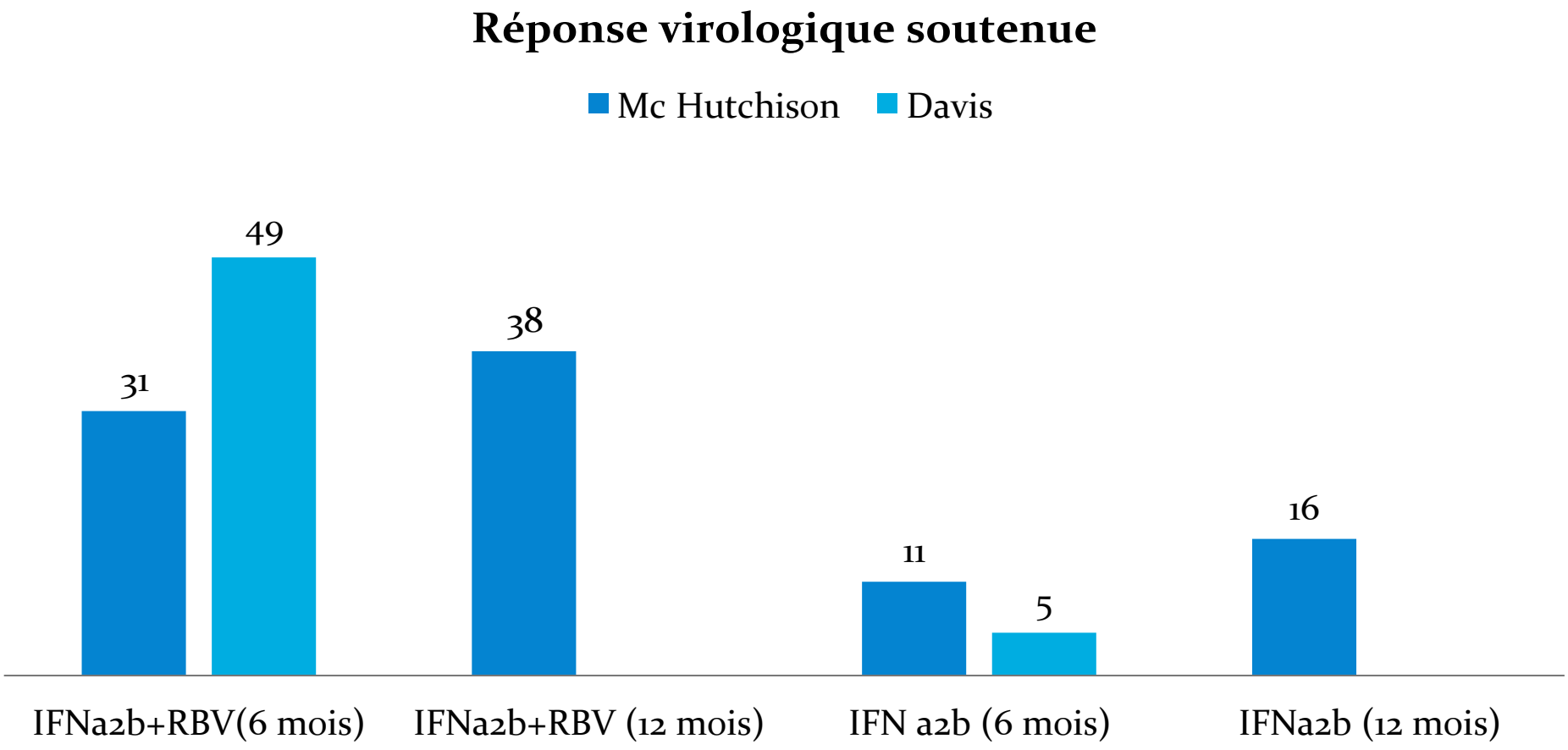
La Ribavirine: Brillanti* porte bien son nom



* 10 malades dans chaque groupe

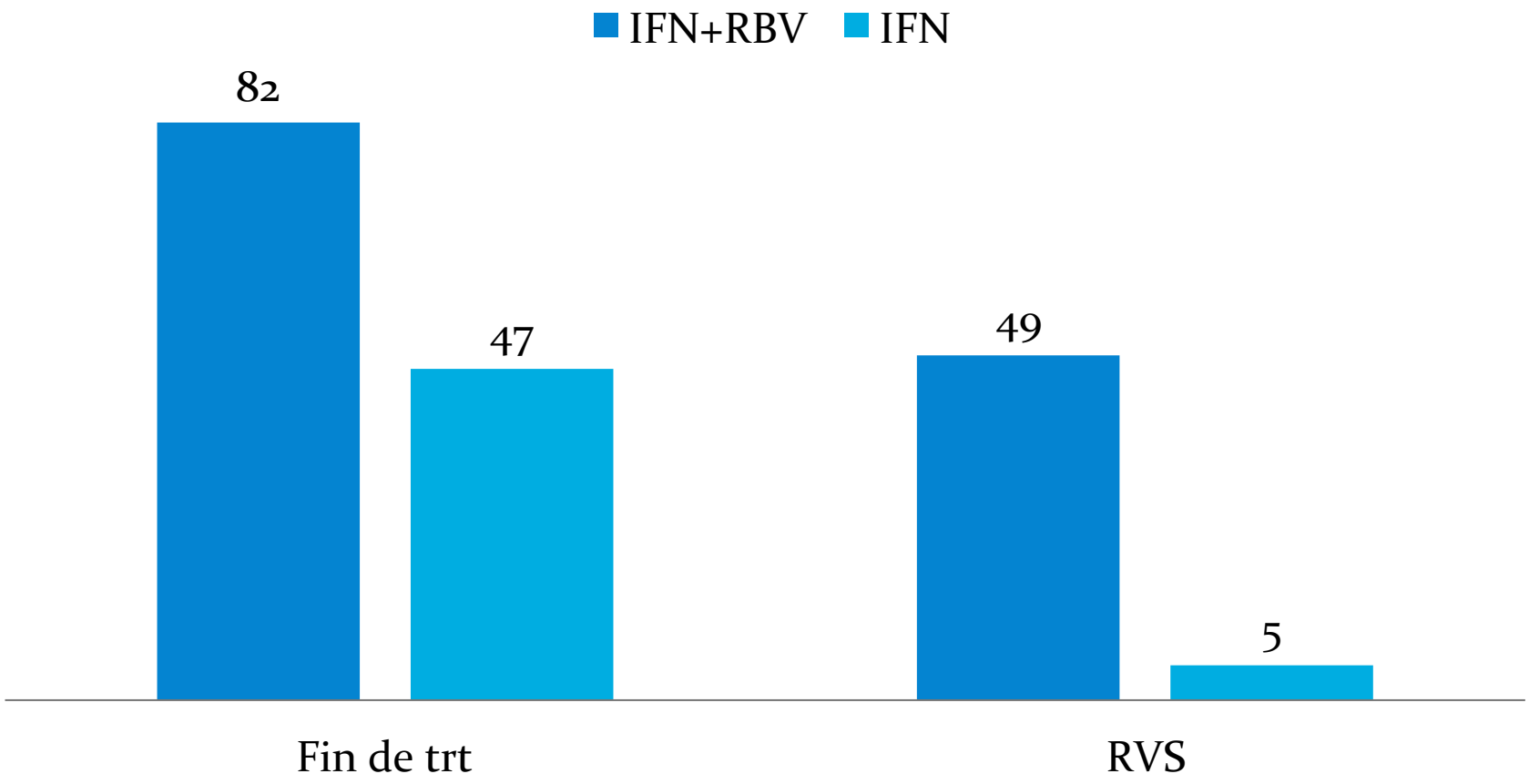
Brillanti et al, Gastroenterology 1994

IFNa2b+Ribavirine: naïfs



Davis et al, NEJM 1998; Mc Hutchison NEJM 1998

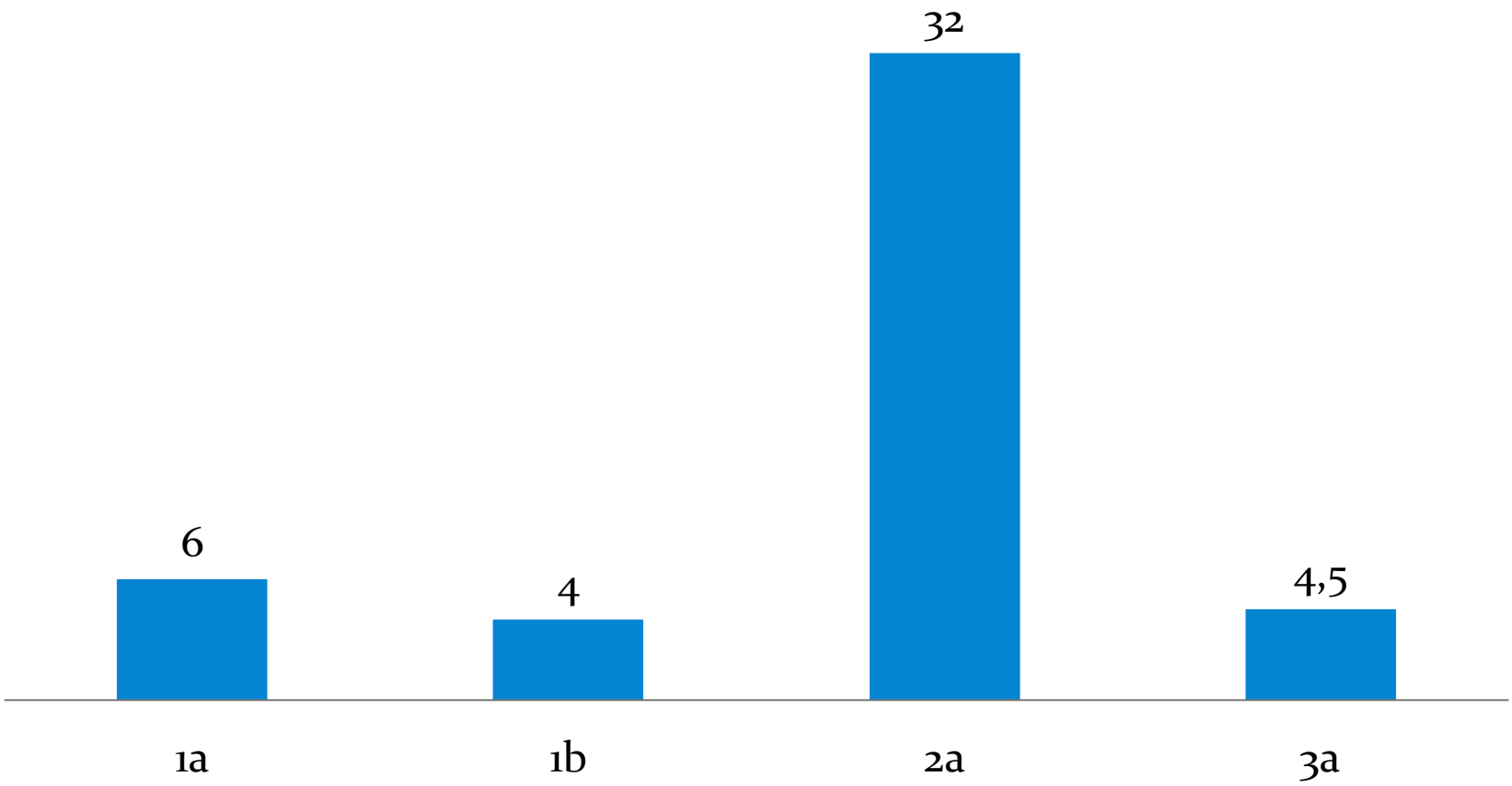
Interféron a2b+Ribavirine: rechuteurs



- 345 rechuteurs à IFN seul
- Trt 6 mois; RBV:1000-1200mg/j

Davis et al, NEJM 1998

Le génotype

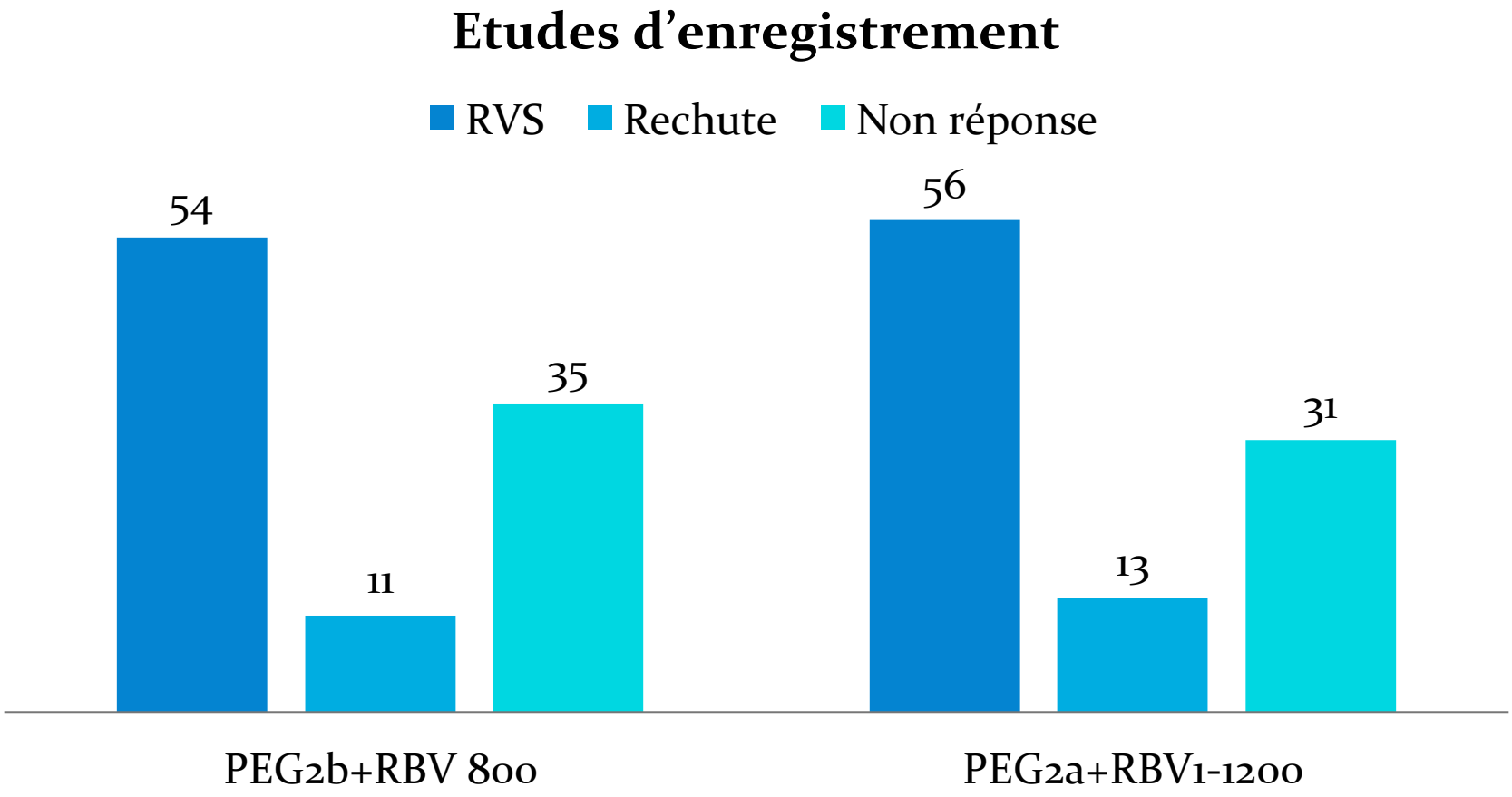


Nousbaum Ann Intern Med 1994; Martinot-Peignoux et al, Hepatology 1995

Les années 2000:
Le PEG et les algorithmes

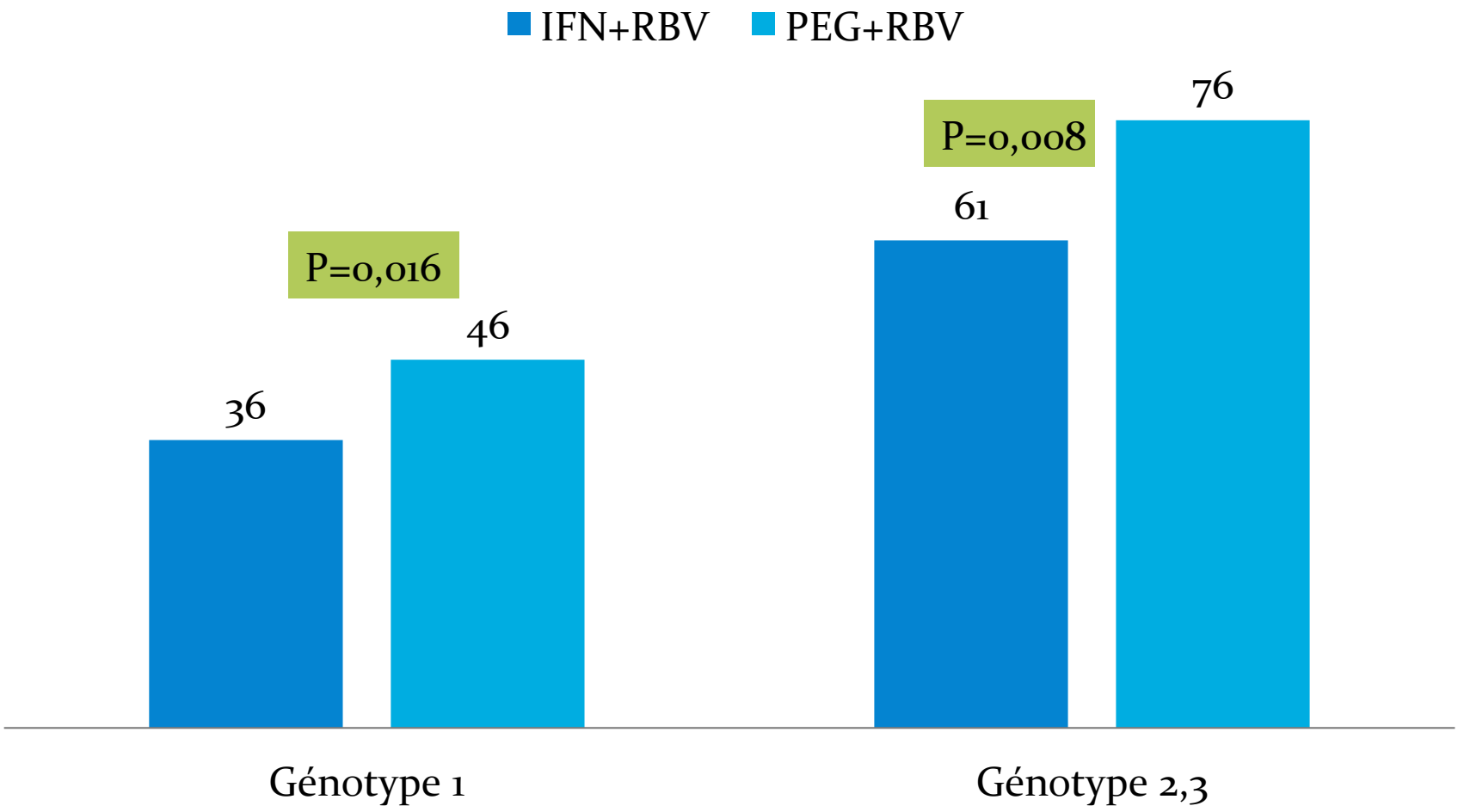
Les accords de Camp David

PEG-IFNα+Ribavirine: Sujets naïfs



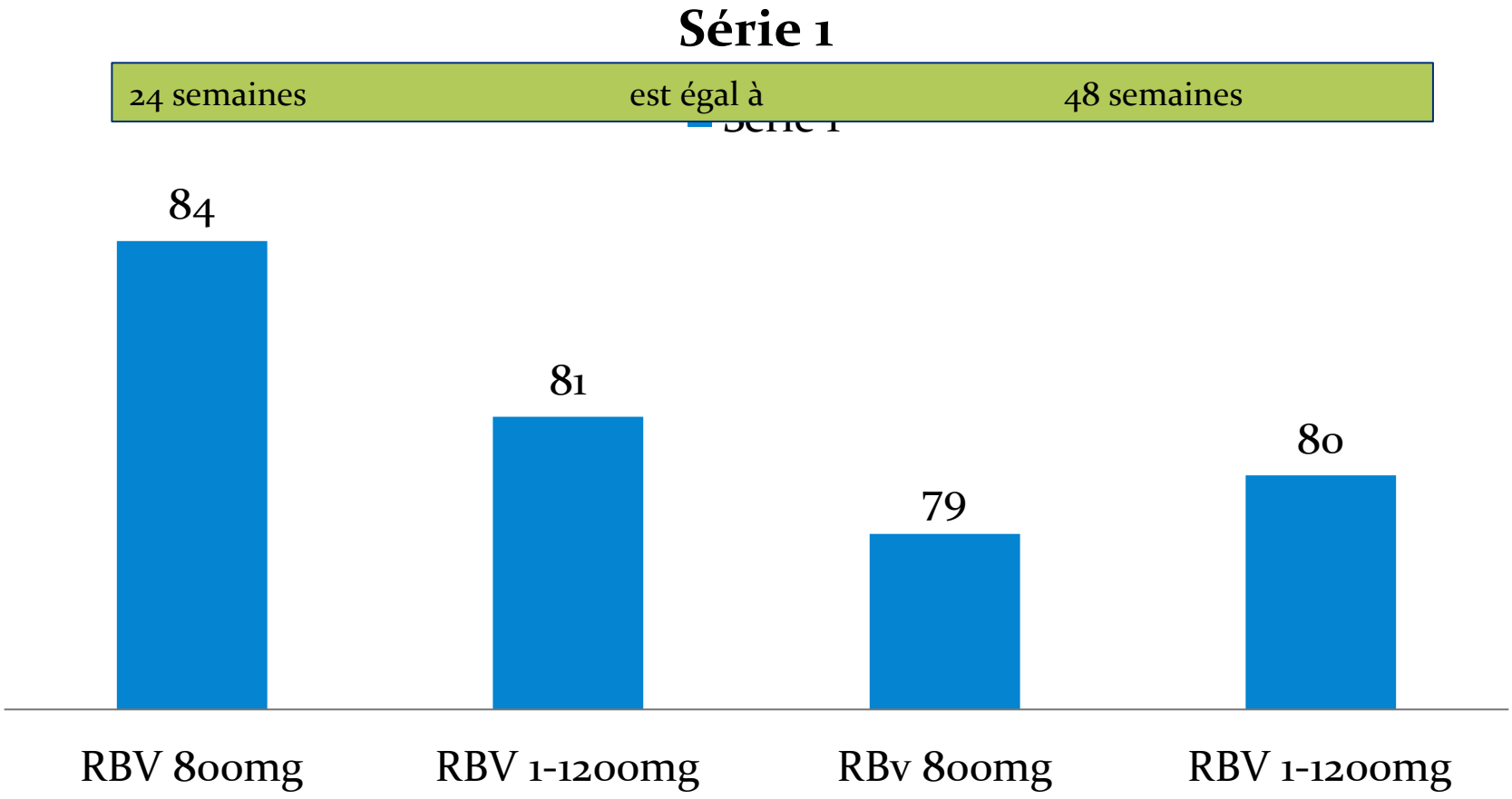
Manns et al, Lancet 2001; Fried et al, NEJM 2002

PEG-IFN α2a+ Ribavirine sujets naïfs



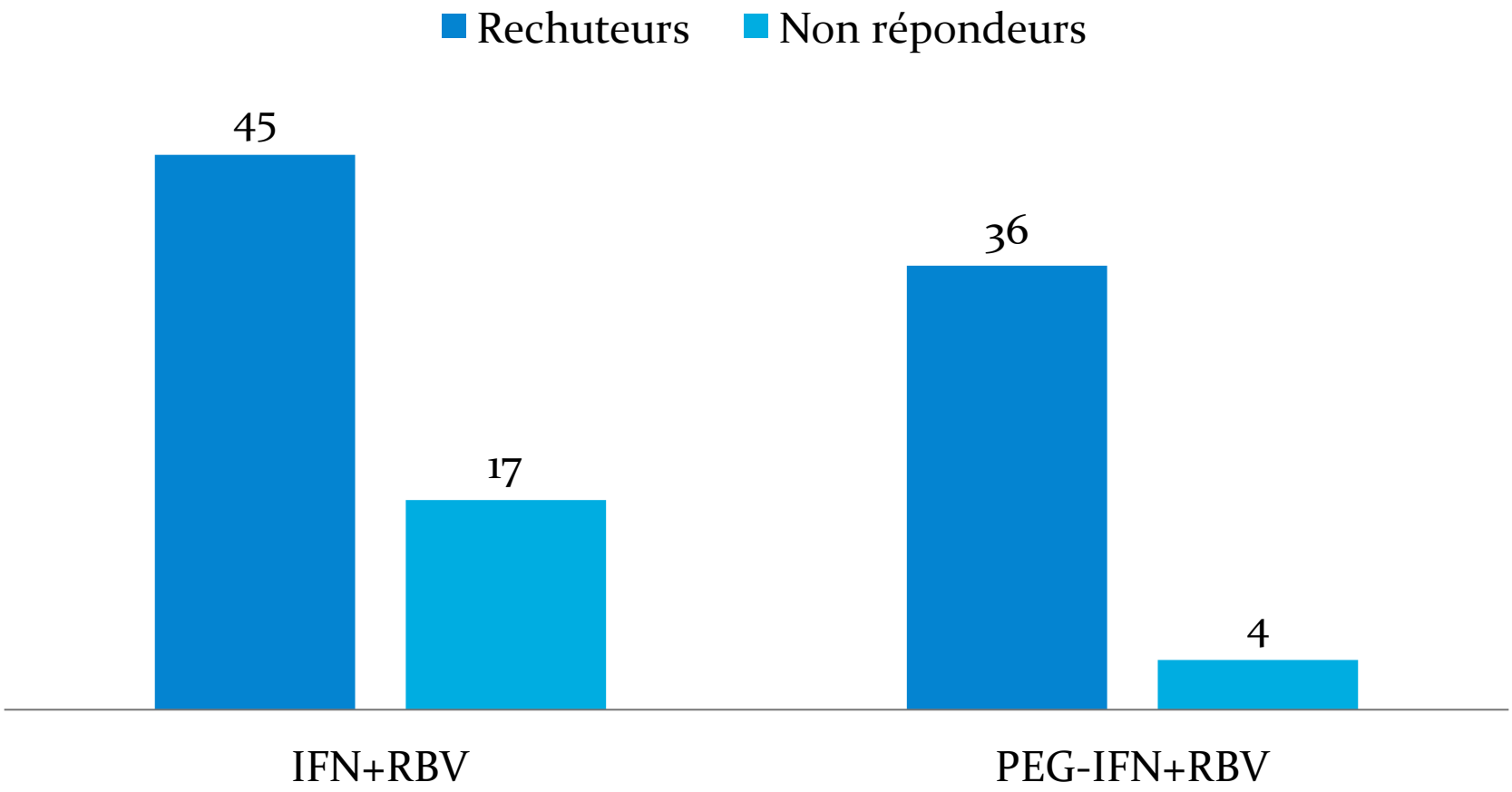
Fried et al, NEJM 2002

IFN PEG a2a+ Ribavirine Génotype 2,3



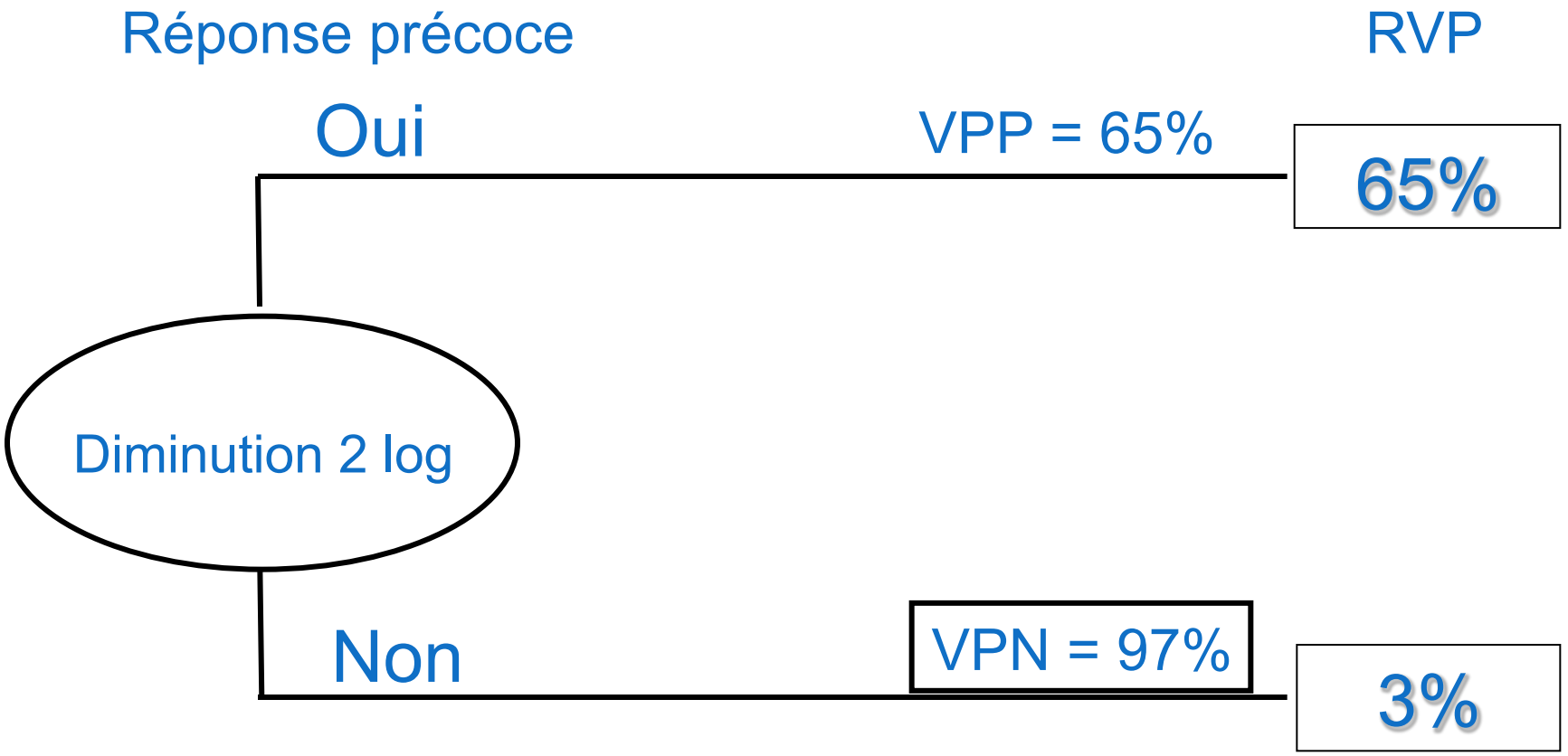
Hadziyannis et al, Ann Intern Med 2004

PEG-IFNα2b+Ribavirine: Rechuteurs et non répondeurs à la bithérapie standard



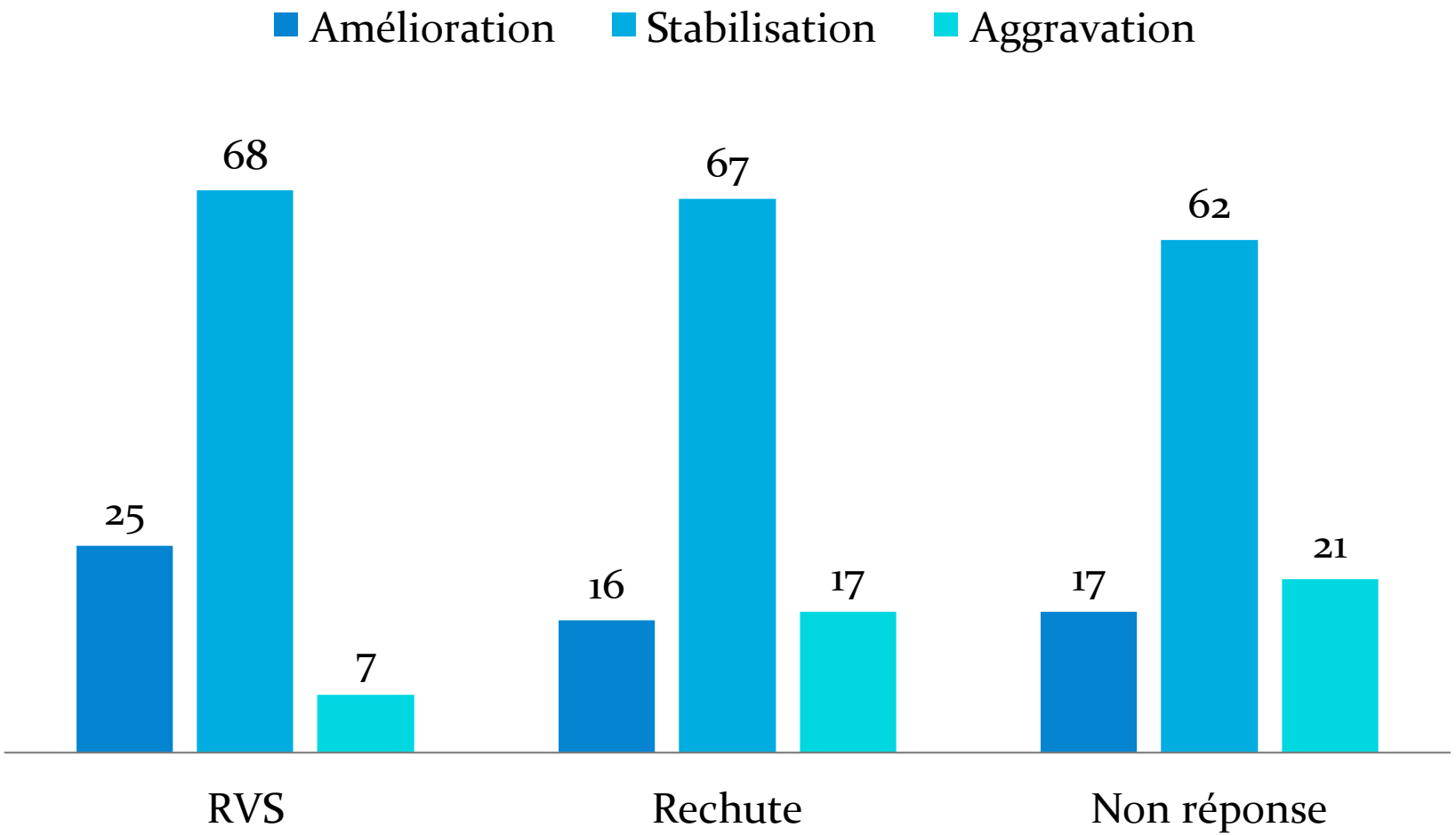
Poynard et al, Gastroenterology 2009

Réponse virologique prolongée selon la réponse précoce (12 semaines)



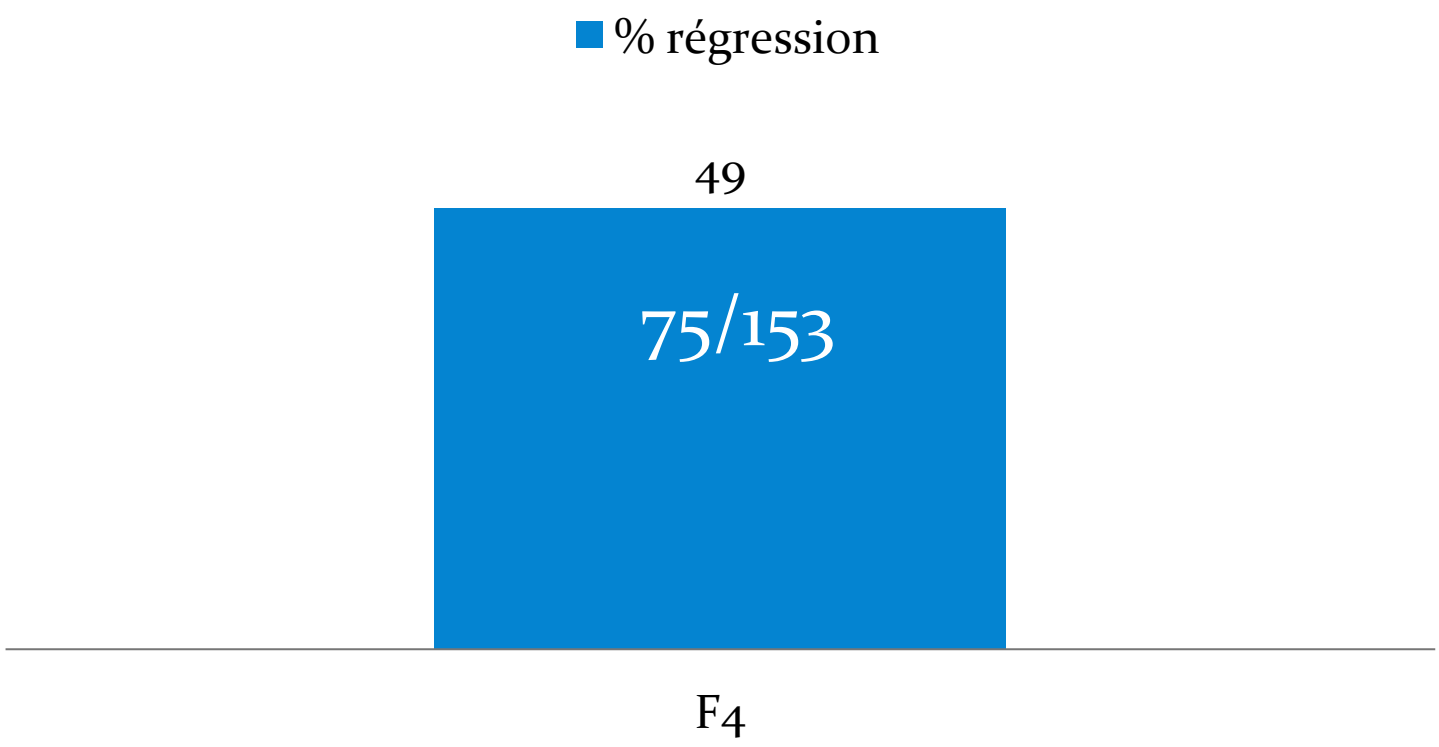
Fried et al. NEJM 2002

La régression de la fibrose



Poynard et al, Gastroenterology 2002

Et surtout la réversion de la cirrhose



Poynard et al, Gastroenterology 2002

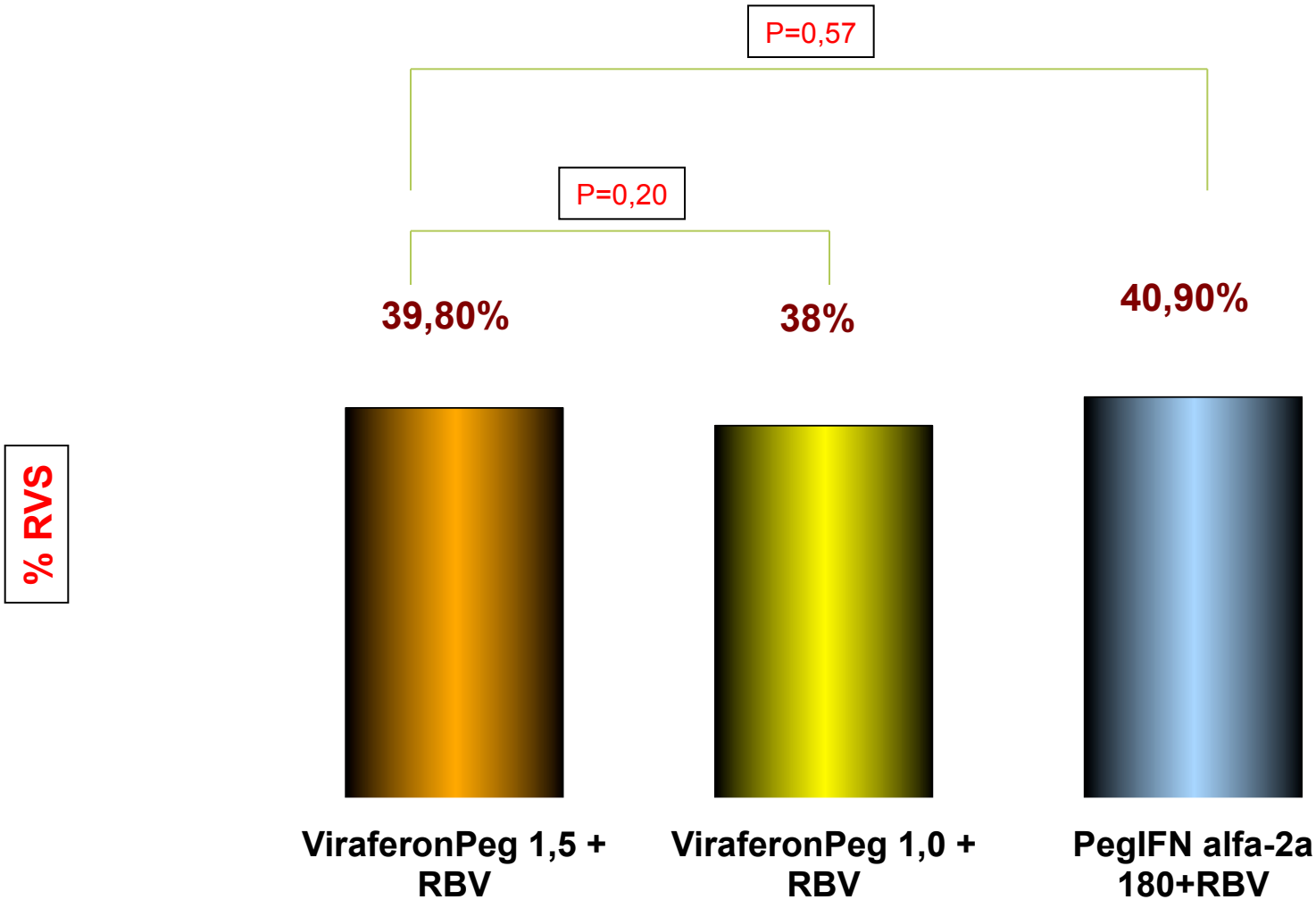
La fin des années 2000:

PEG-α2a versus PEG-α2b? Le traitement d'entretien? La génétique?

2008

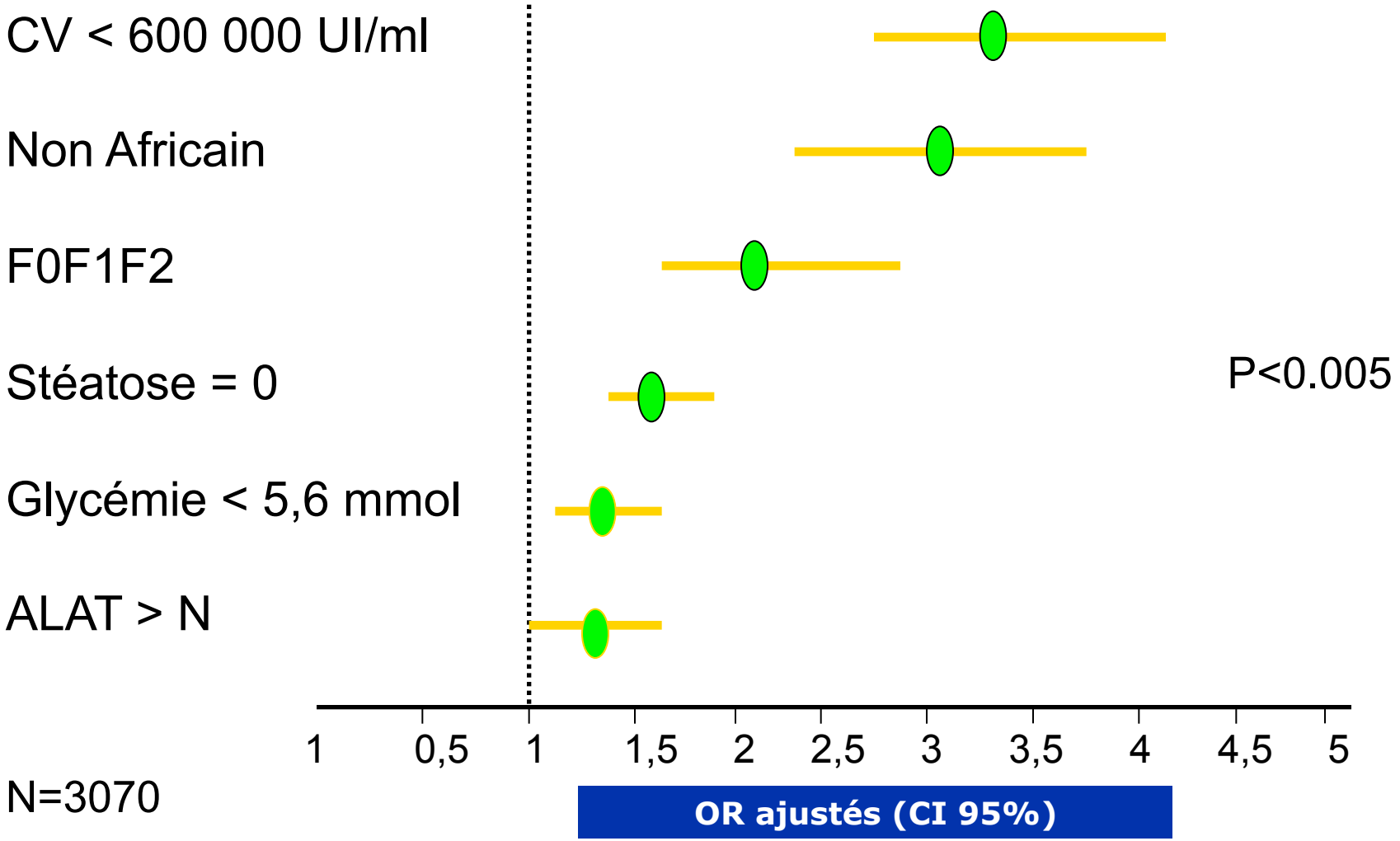
2007

Génotype 1 : essai IDEAL



Mc Hutchison et al. N Engl J Med 2009

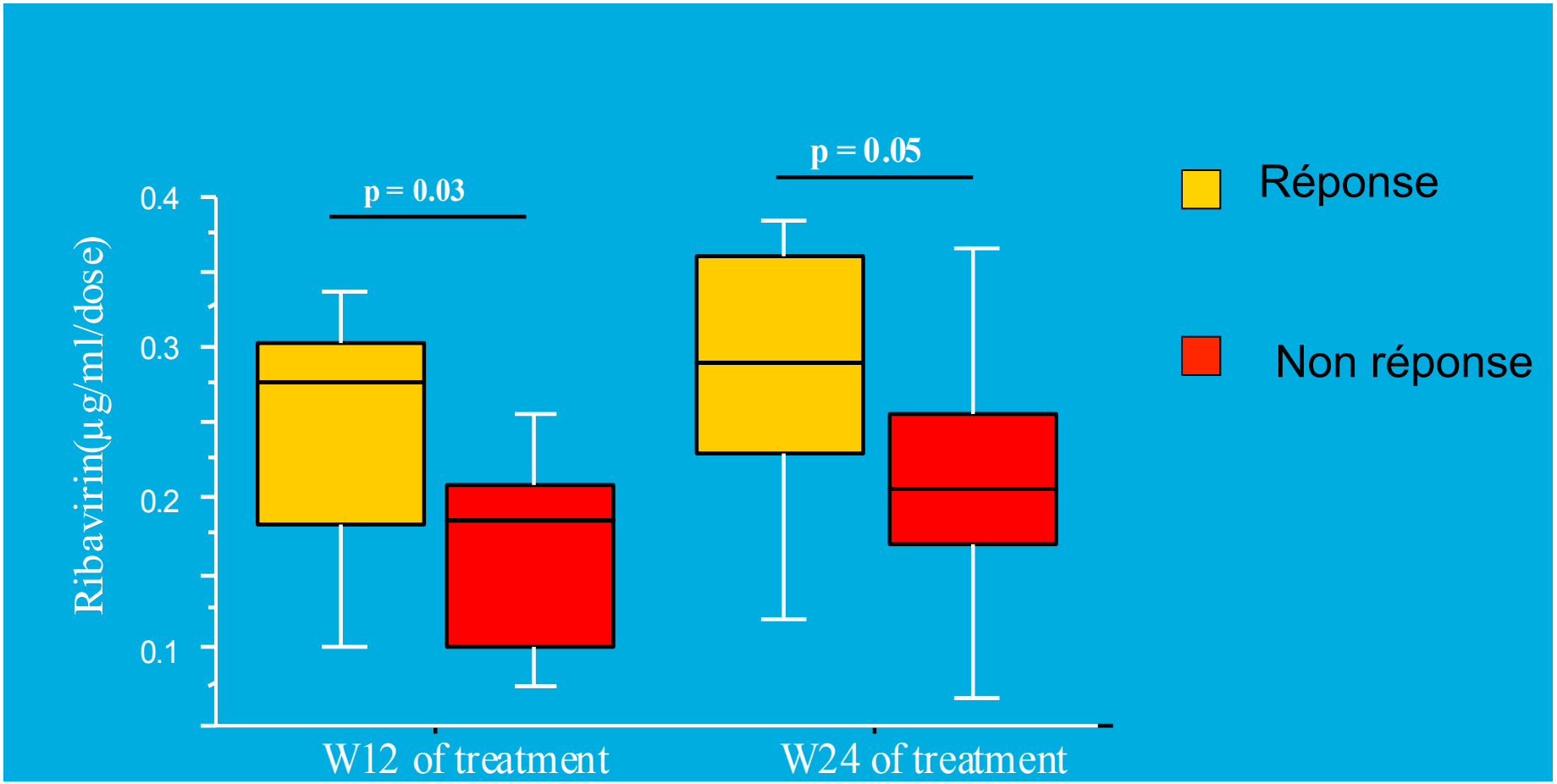
Etude IDEAL : analyse multivariée



N=3070

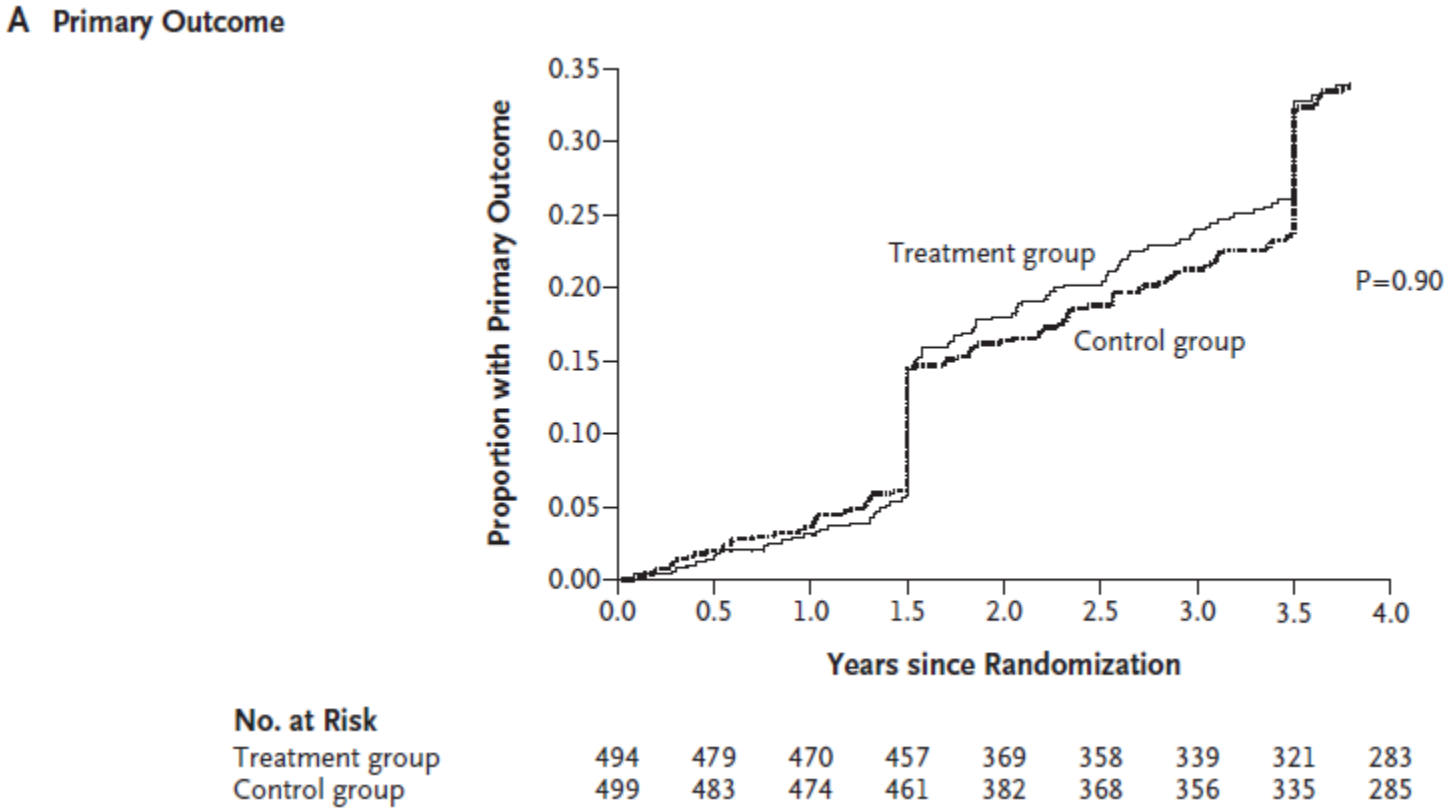
McHutchison et al. NEJM 2009

Impact de la concentration de ribavirine



Larrat et al. Antimicrobial Agent Chemother 2003

Le traitement de maintenance?

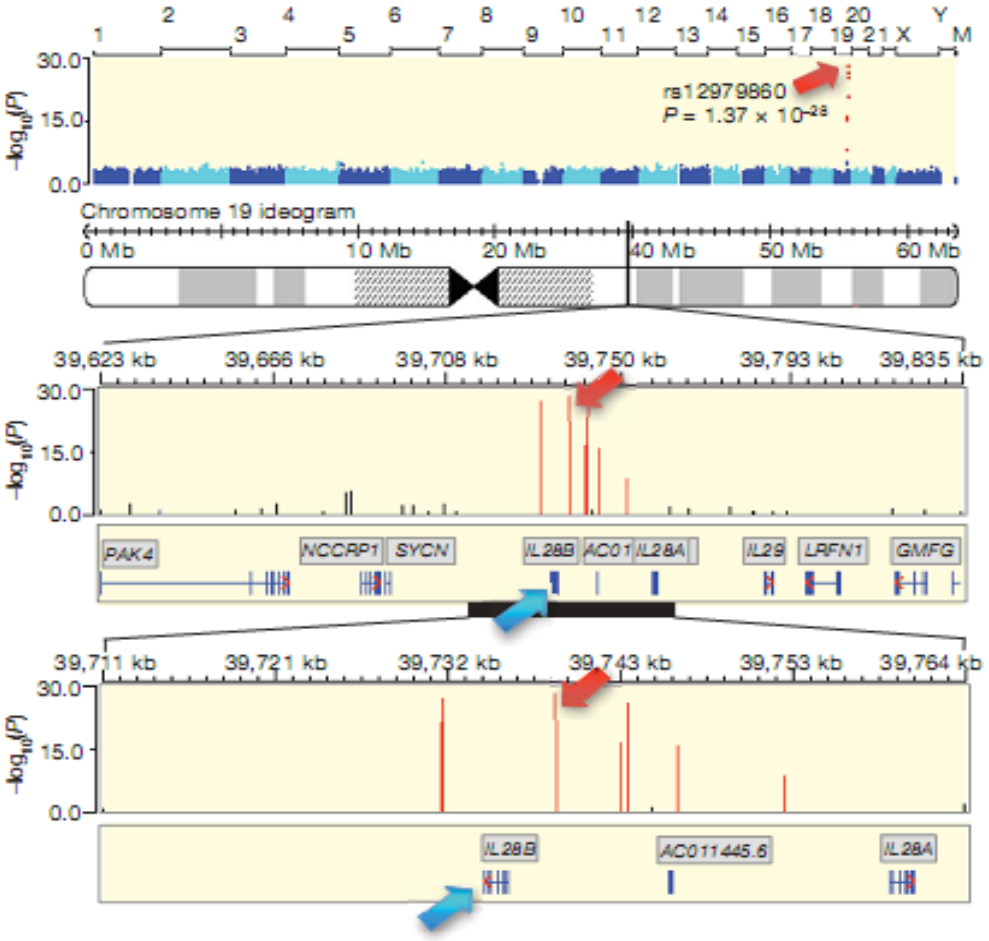


*PEG-IFN a-2a 90µg; 3,5 ans

Di Bisceglie et al, NEJM 2008

Prédiction génétique de la RVS

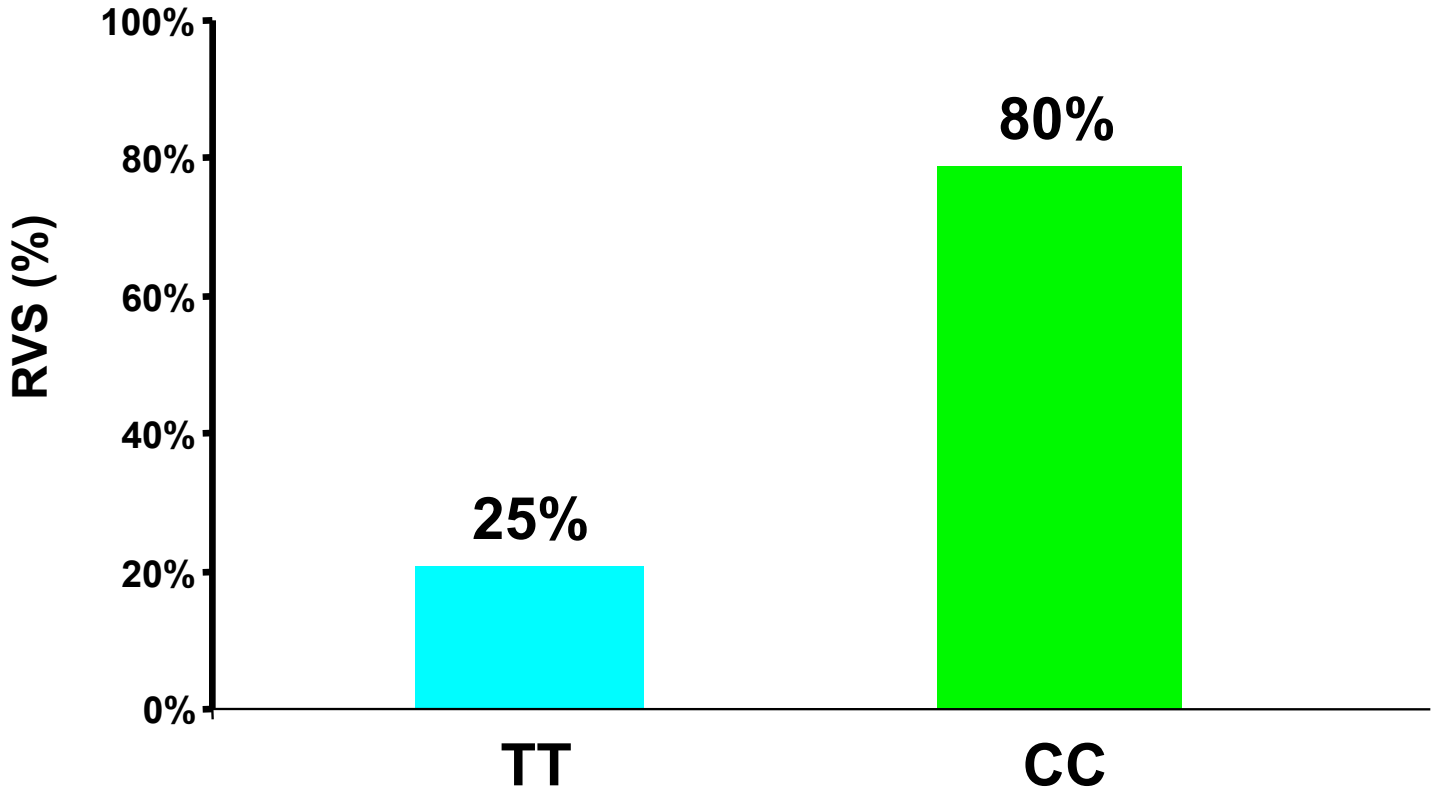
- 1 628 malades
- Étude pan-génomique
- Recherche de SNP
- polymorphisme
- « rs 12979860 » lié à la RVS
- gène de l'IL28B (IFN λ-3)
  - 2 allèles (C et T)



Ge D et al, Nature 2009

Prédiction de la RVS par le polymorphisme génétique

Génomique (C/T)



Ge et al.. Nature 2009

Les années 2010: Les a

2012

2017

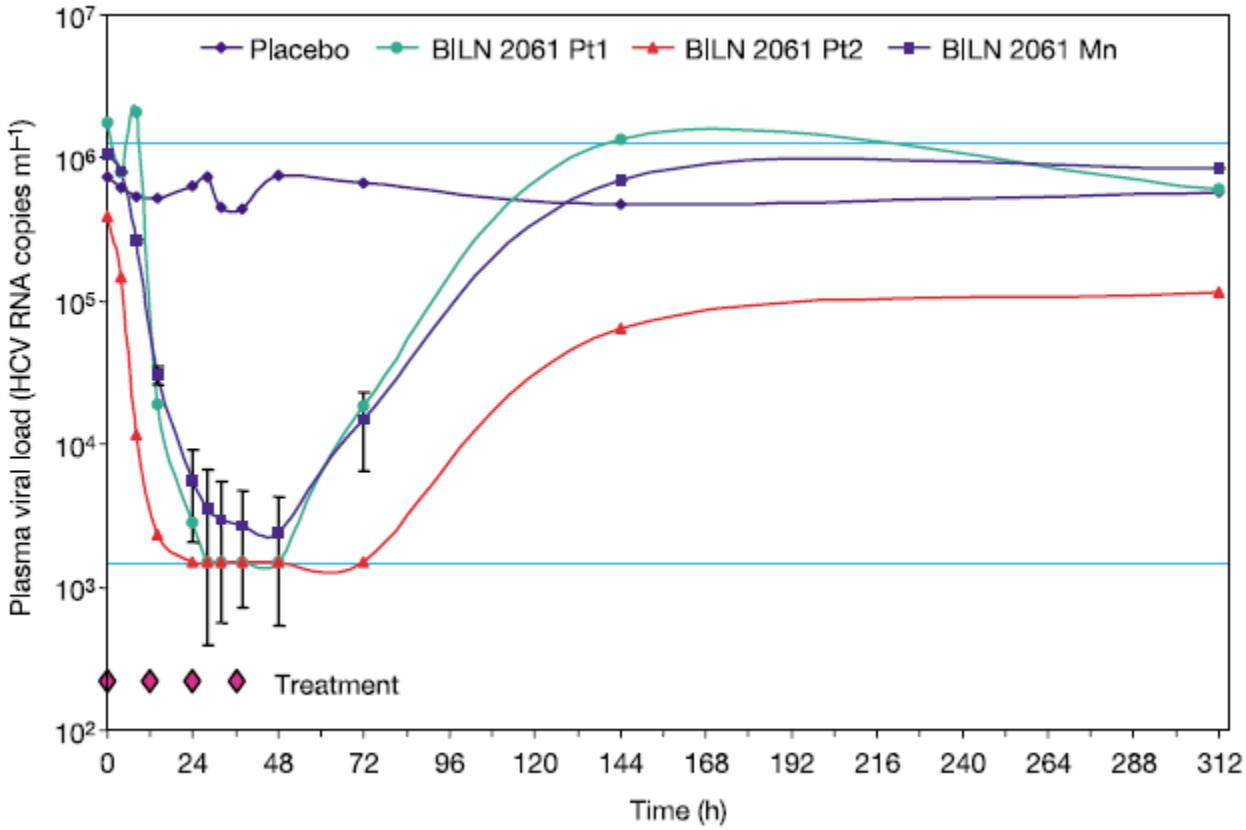
L'arrivée des antiviraux directs

An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus

Daniel Lamarre[1], Paul C. Anderson[2], Murray Bailey[2], Pierre Beaulieu[2], Gordon Bolger[1], Pierre Bonneau[1], Michael Bös[2], Dale R. Cameron[2]*, Mireille Cartier[1], Michael G. Cordingley[1], Anne-Marie Faucher[2], Nathalie Goudreau[2], Stephen H. Kawai[2], George Kukolj[1], Lisette Lagacé[1], Steven R. LaPlante[2], Hans Narjes[3], Marc-André Poupart[2], Jean Rancourt[2], Roel E. Sentjens[4], Roger St George[5], Bruno Simoneau[2], Gerhard Steinmann[3], Diane Thibeault[1], Youla S. Tsantrizos[2], Steven M. Weldon[5], Chan-Loi Yong[5] & Montse Llinàs-Brunet[2]

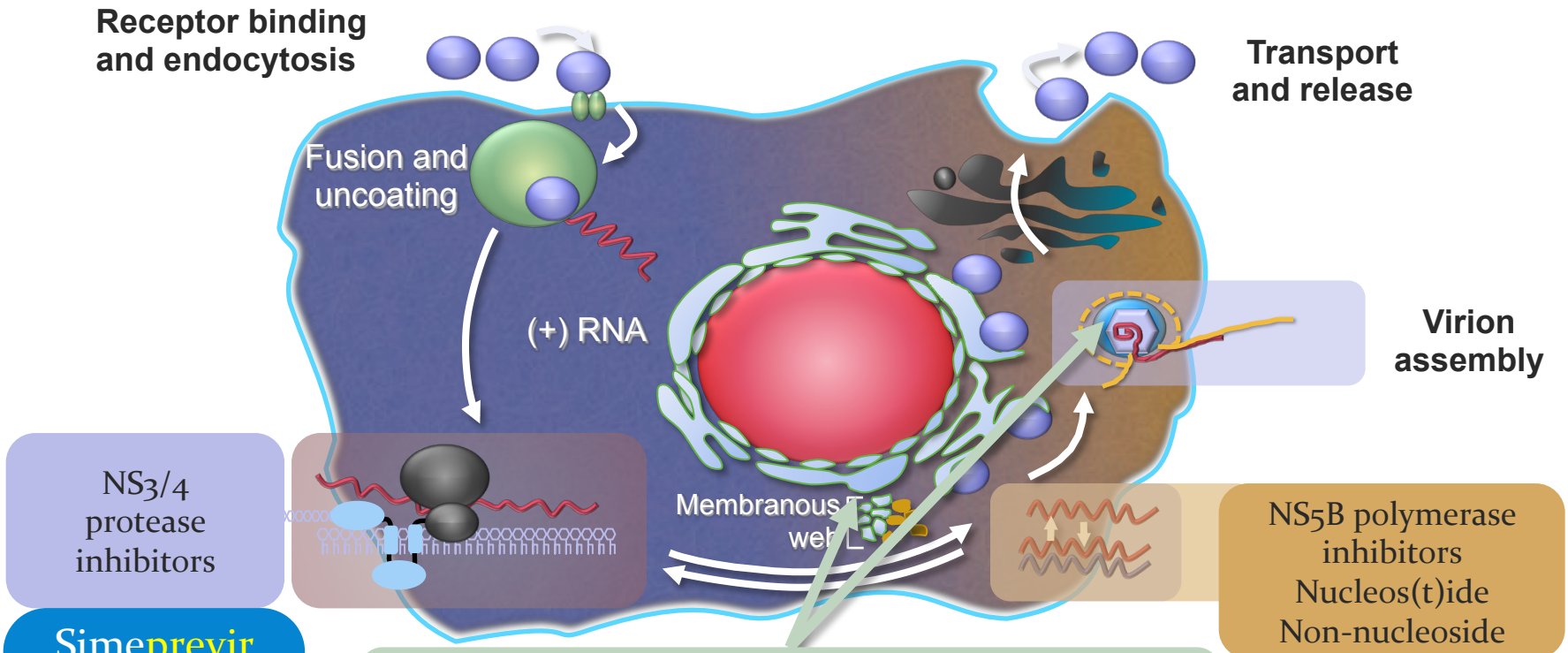
Lamarre et al, Nature 2003

BILN 2061



Lamarre et al, Nature 2003

Cycle viral Du VHC: Cibles des nouveaux anti-viraux

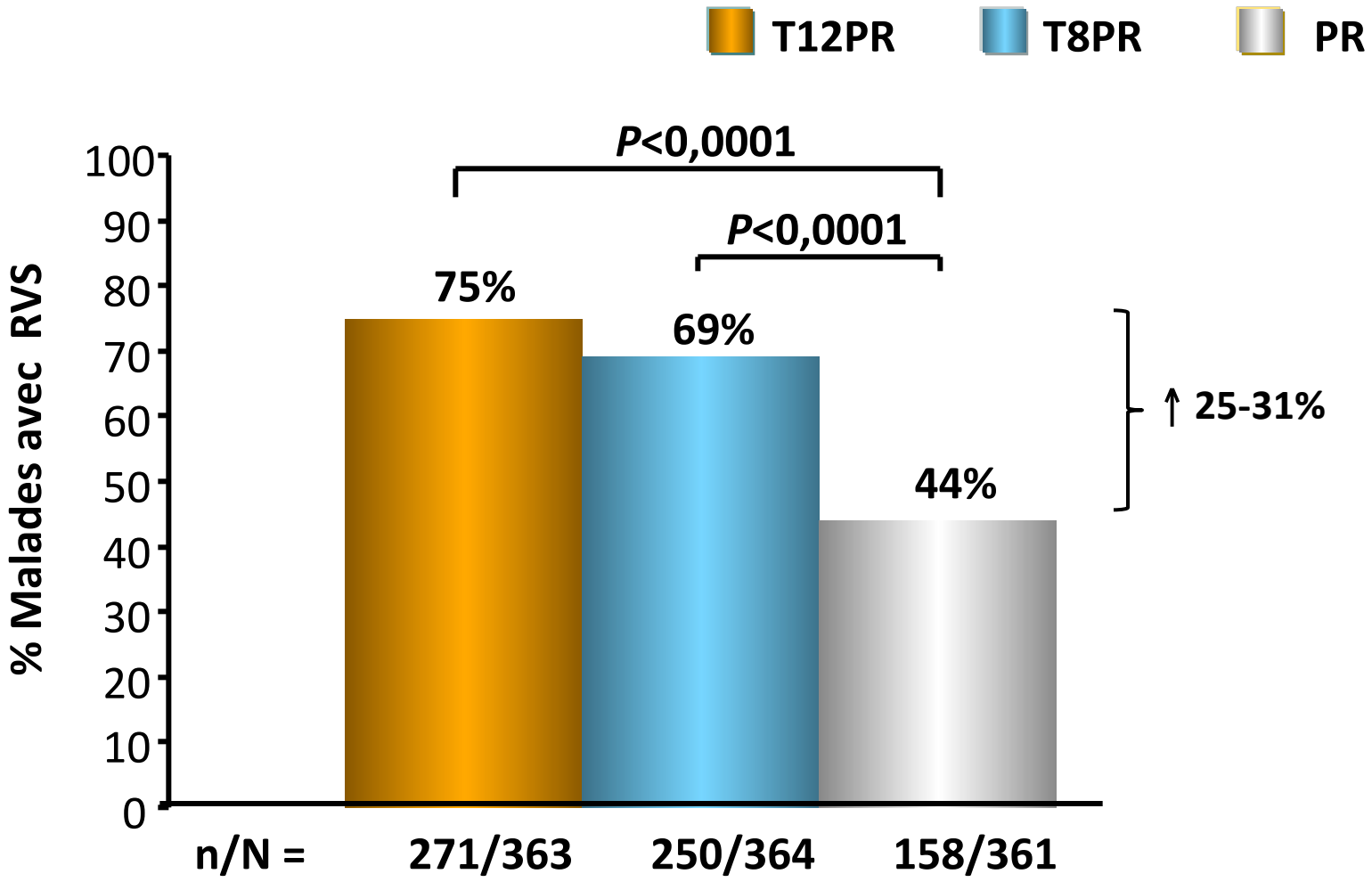


Adapted from Manns MP, et al. Nat Rev Drug Discov. 2007;6:991–1000.

1ers Inhibiteurs de Protéase NS3 en Développement Clinique*

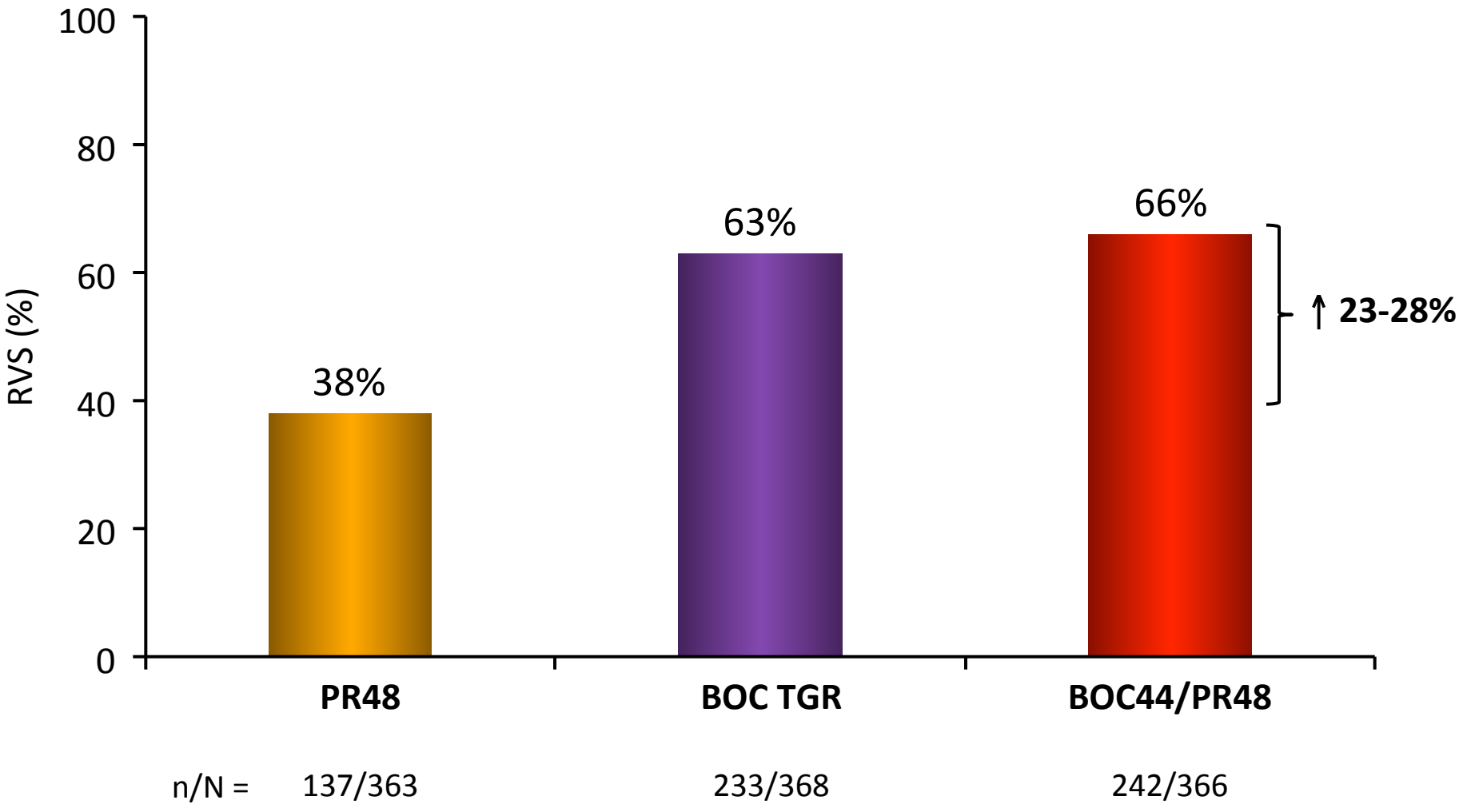
- Telaprevir (Incivo®, Janssen)
- Boceprevir (Victrélis®, MSD)
- Siméprévir (Tibotec, Janssen))

TELAPREVIR: RVS



Jacobson IM, et al. NEJM 2011

BOCEPREVIR: RVS

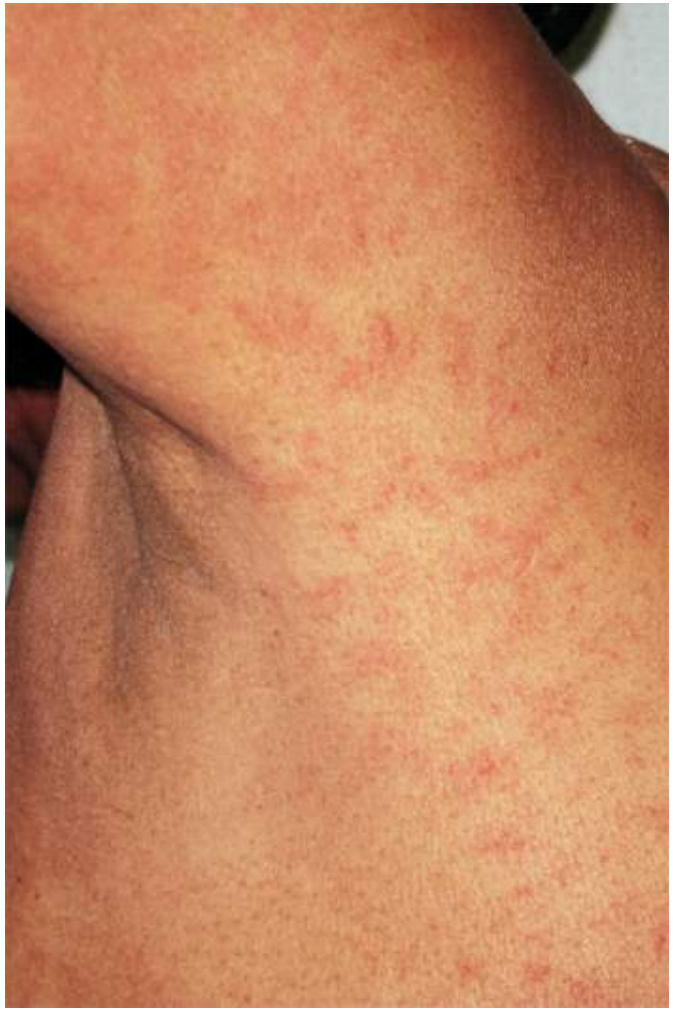


Poordad F, et al. N Engl J Med. 2011

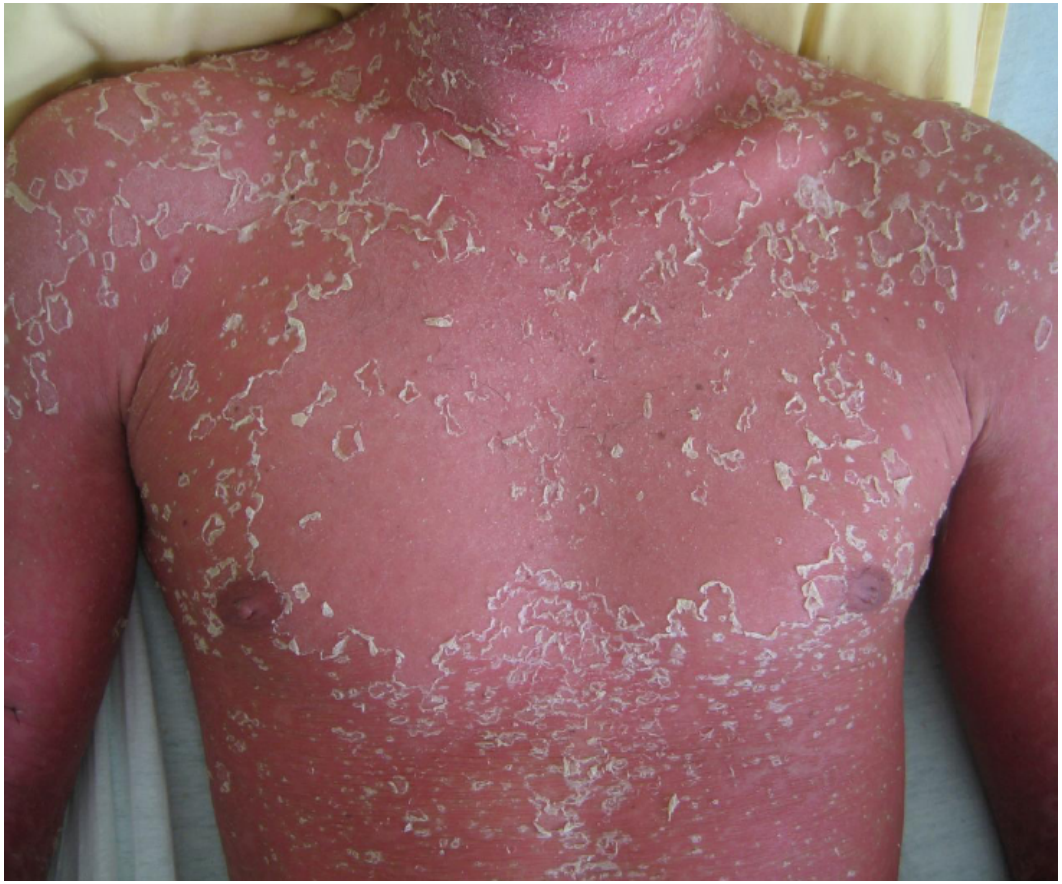
Effets indésirables

Effet II	PR+Télaprévir	PR+Bocéprévir	PR
Prurit	45-52%	--	27-36%
Rash (sévère)	35-37% 6%	14-17%	17-37%
Prurit anal	26%	--	6%
EPO	21%	41-46%	21-24%
Anémie: (10g/dl) (<8,5g/dl)	 36% (9%)	 41-45% (9%)	 14-26% (2-4%)
Arrêt	14%	16%	4-16%

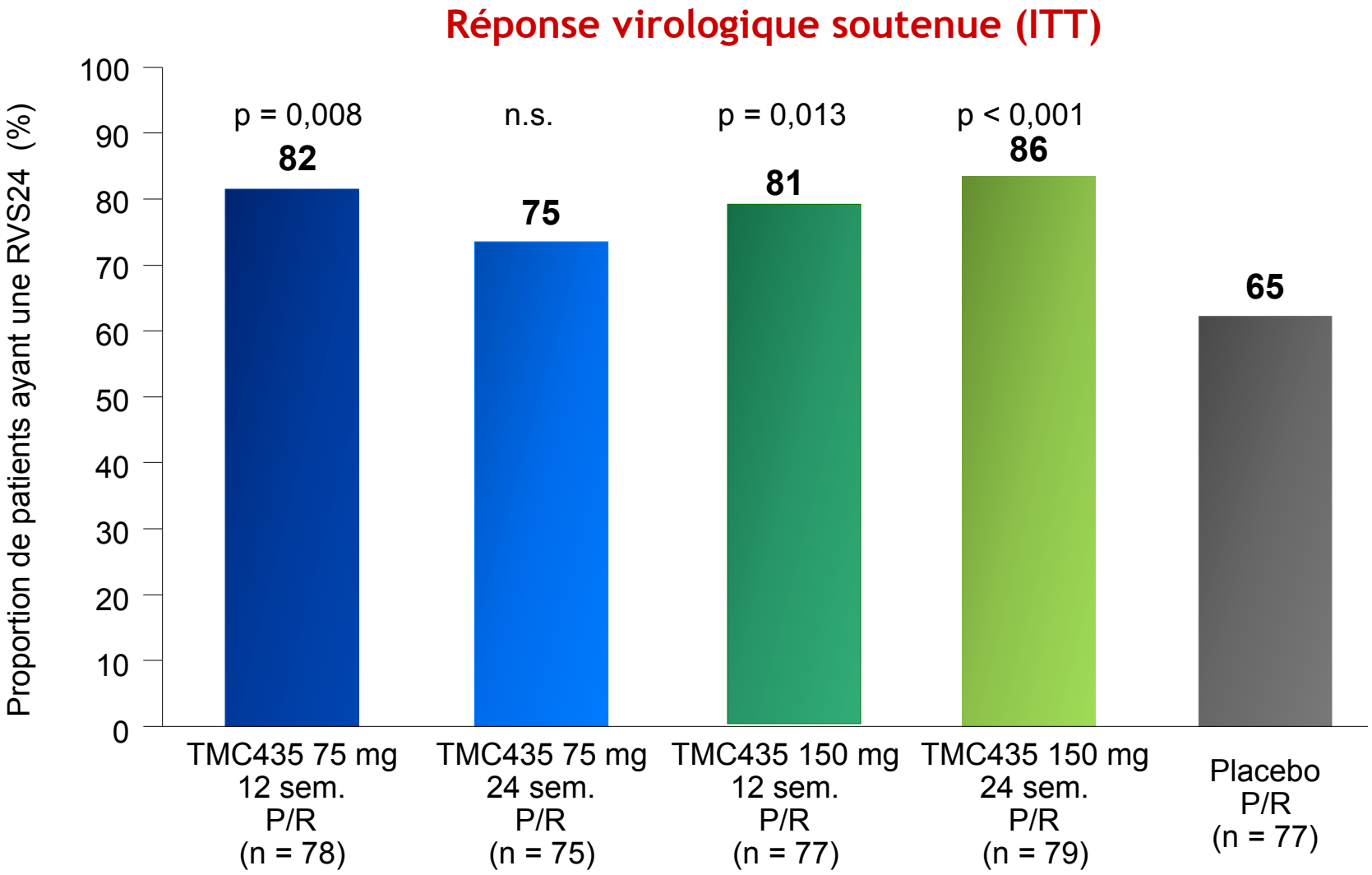
On devient dermatologue: Gravité de l'éruption cutanée



Dress syndrome



SIMEPREVIR: Génotype 1



Fried et al, Hepatology 2013

Les progrès:

1. **I. Protéase puissants de 2ème génération (Prévir)**
2. **Anti-NS5a (Asvir)**
3. **Anti NS5b (Buvir)**
4. **On abandonne progressivement l'Interferon**

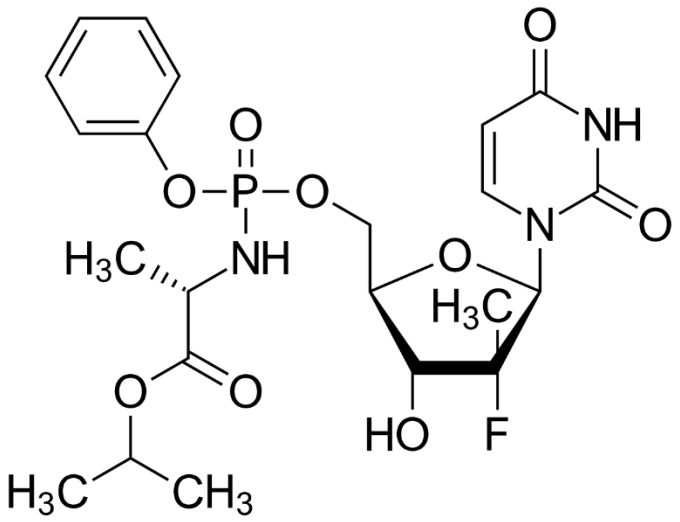
La Révolution: le Sofosbuvir

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2010, p. 3187–3196 Vol. 54, No. 8
0066-4804/10/$12.00 doi:10.1128/AAC.00399-10

PSI-7851, a Pronucleotide of β-D-2′-Deoxy-2′-Fluoro-2′-*C*-Methyluridine Monophosphate, Is a Potent and Pan-Genotype Inhibitor of Hepatitis C Virus Replication▽

Angela M. Lam,[1]* Eisuke Murakami,[1] Christine Espiritu,[1] Holly M. Micolochick Steuer,[1] Congrong Niu,[1] Meg Keilman,[1] Haiying Bao,[1] Veronique Zennou,[1] Nigel Bourne,[2] Justin G. Julander,[3] John D. Morrey,[3] Donald F. Smee,[3] David N. Frick,[4] Julie A. Heck,[4] Peiyuan Wang,[1] Dhanapalan Nagarathnam,[1] Bruce S. Ross,[1] Michael J. Sofia,[1] Michael J. Otto,[1] and Phillip A. Furman[1]*

Pharmasset, Inc., 303A College Road East, Princeton, New Jersey 08540[1]; University of Texas Medical Branch, Galveston, Texas 77555[2]; Institute for Antiviral Research, Department of Animal, Dairy and Veterinary Sciences, Utah State University, Logan, Utah 84322[3]; and Department of Biochemistry and Molecular Biology, New York Medical College, Valhalla, New York 10595[4]



Pharmasset → Gilead **11 Milliards$**

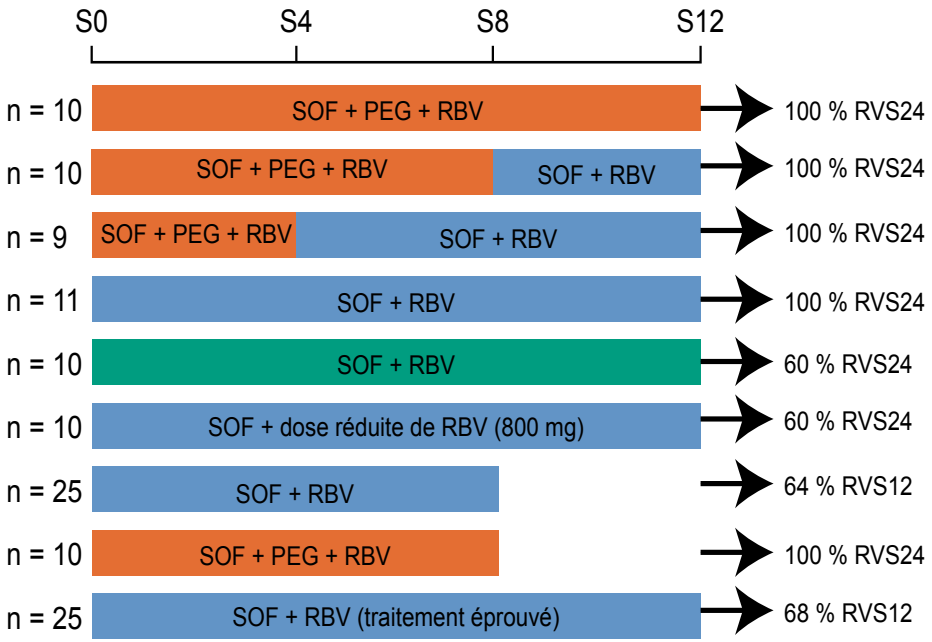
Inhibiteurs de la Polymérase

- **Nucléosidiques:**
- **NS5b:**
  - Analogues de substrats naturels
  - NS5b: très conservée
  - Tout génotype
  - Haute barrière de résistance
- **NS5a:**

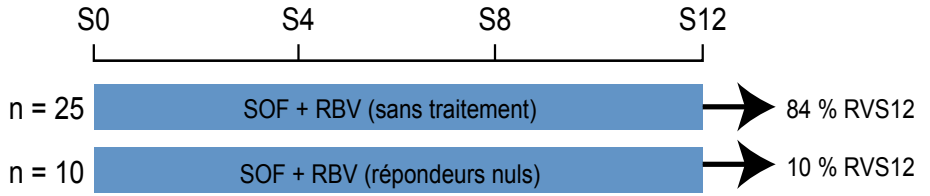
- **Non nucléosidiques**
  - Liaison à 1/5 sites allostériques
  - Changement conformationnel du site catalytique
  - Génotype spécifique
  - Sélection de mutants

Efficacité du Sofosbuvir sur les infections à VHC de génotypes 1, 2 et 3

Cohorte génotypes 2/3



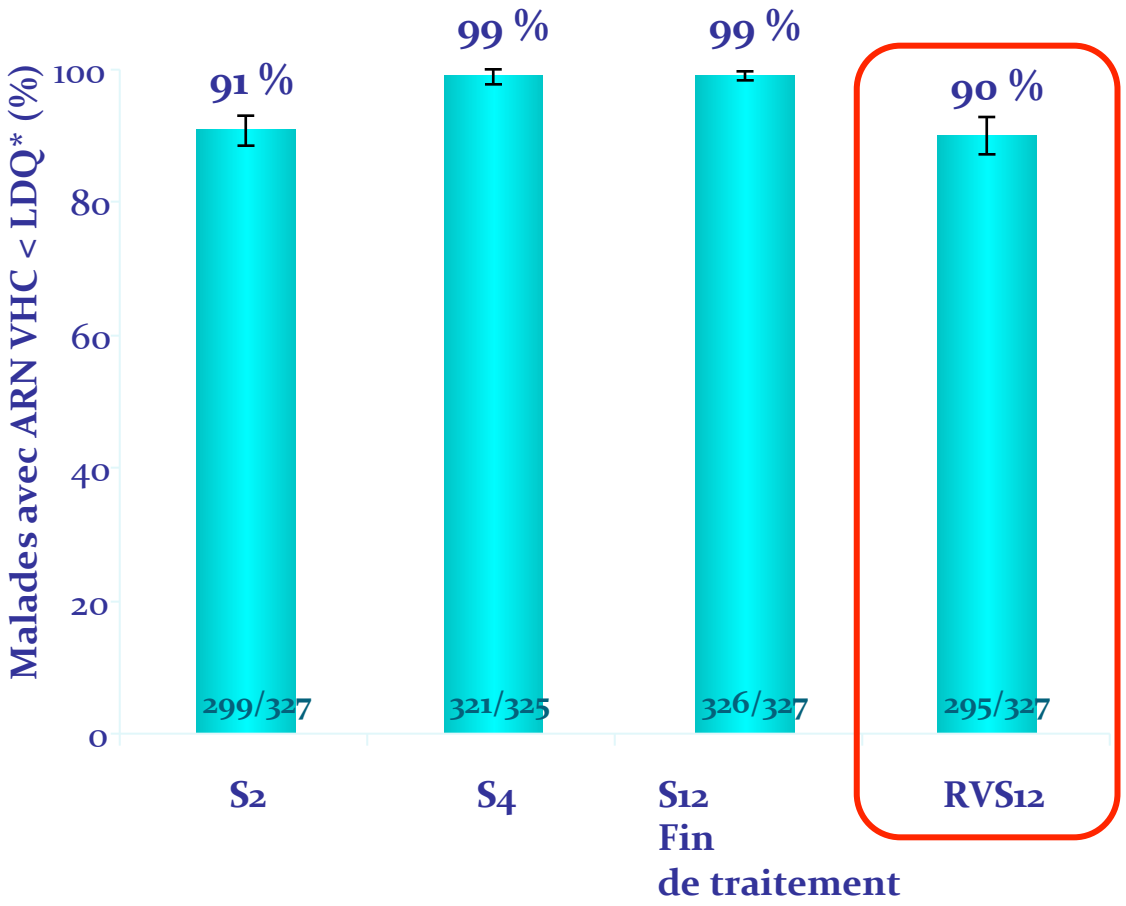
Cohorte génotypes 1



Gane et al, NEJM 2012

Tri-thérapie PR + Sofosbuvir

Réponse virologique

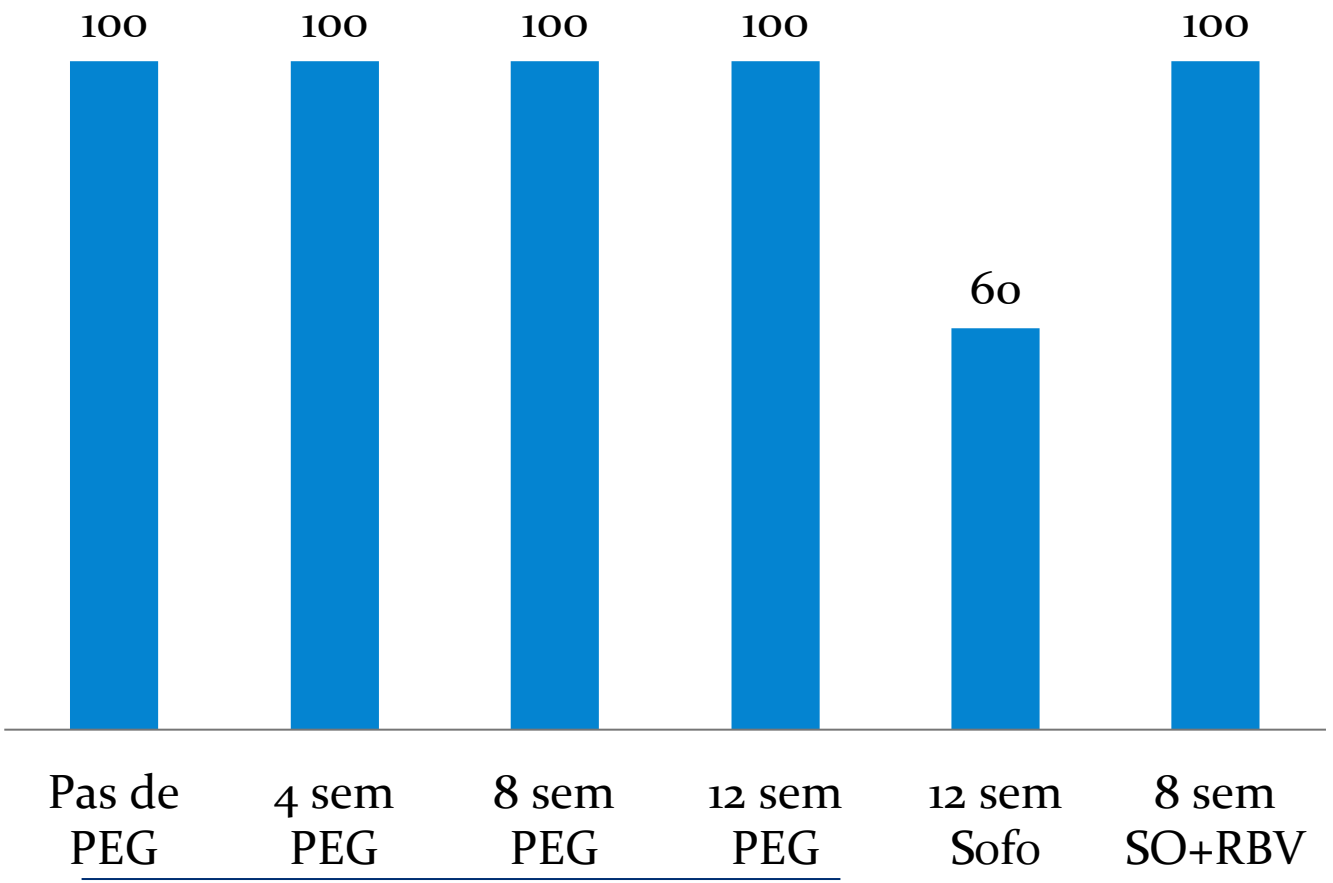


* LDQ : ARN VHC < 25 UI/ml

Lawitz et al, NEJM 2013

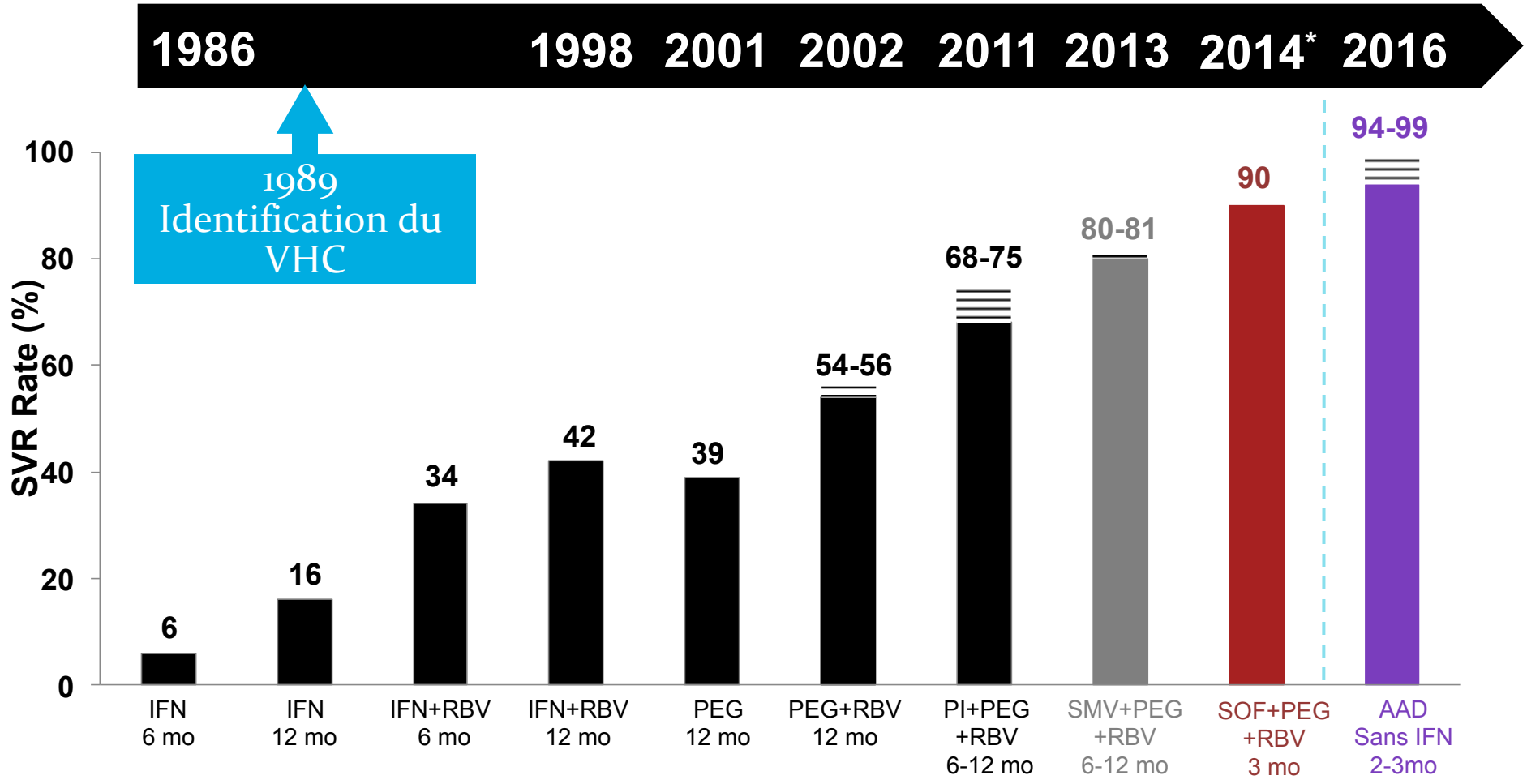
Sofosbuvir ±PR: génotypes 2,3

Réponse virologique soutenue



Gane EJ et al, NEJM 2013

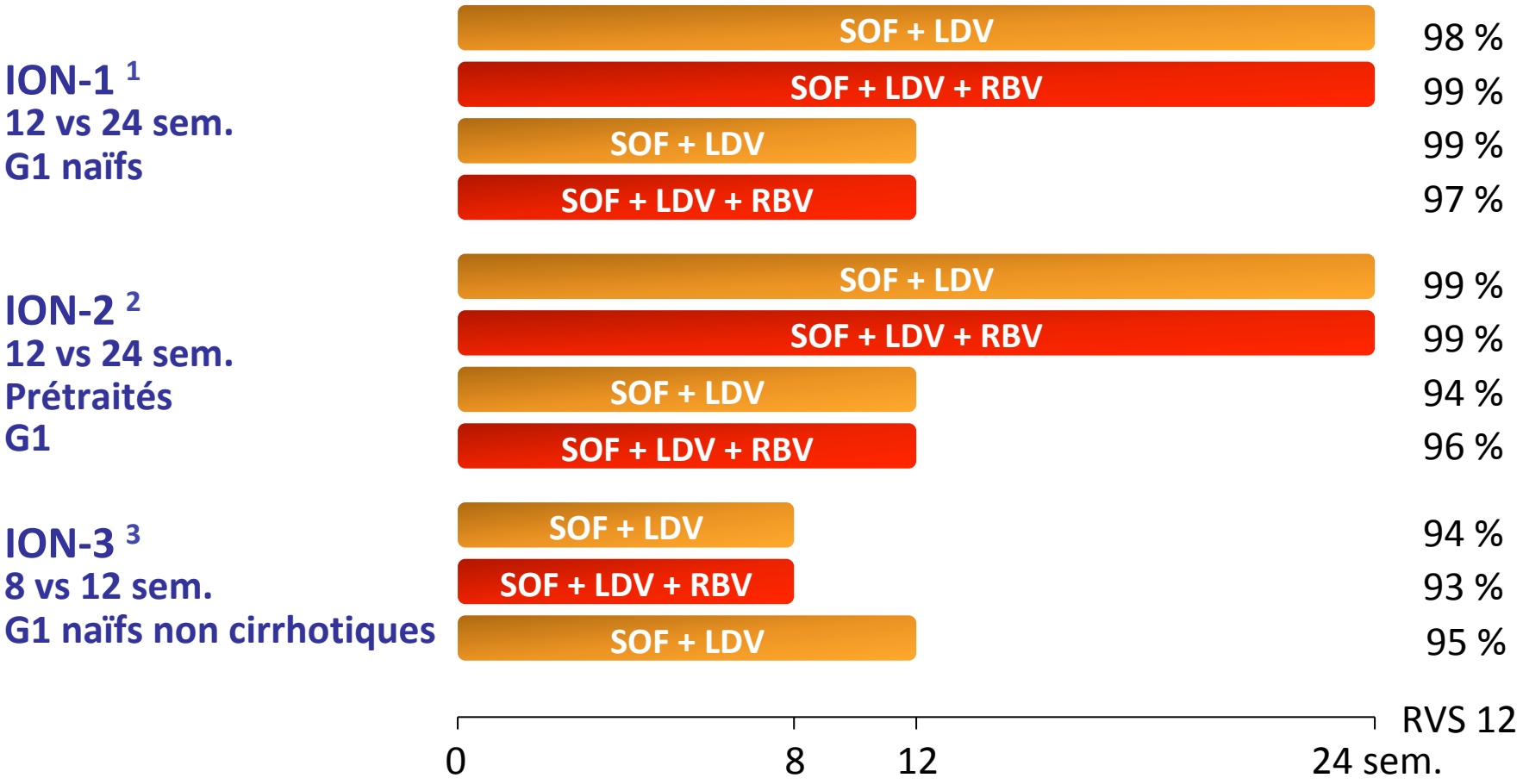
Quels progrès?



Year of data presentation at EASL 2014 and publication in *NEJM

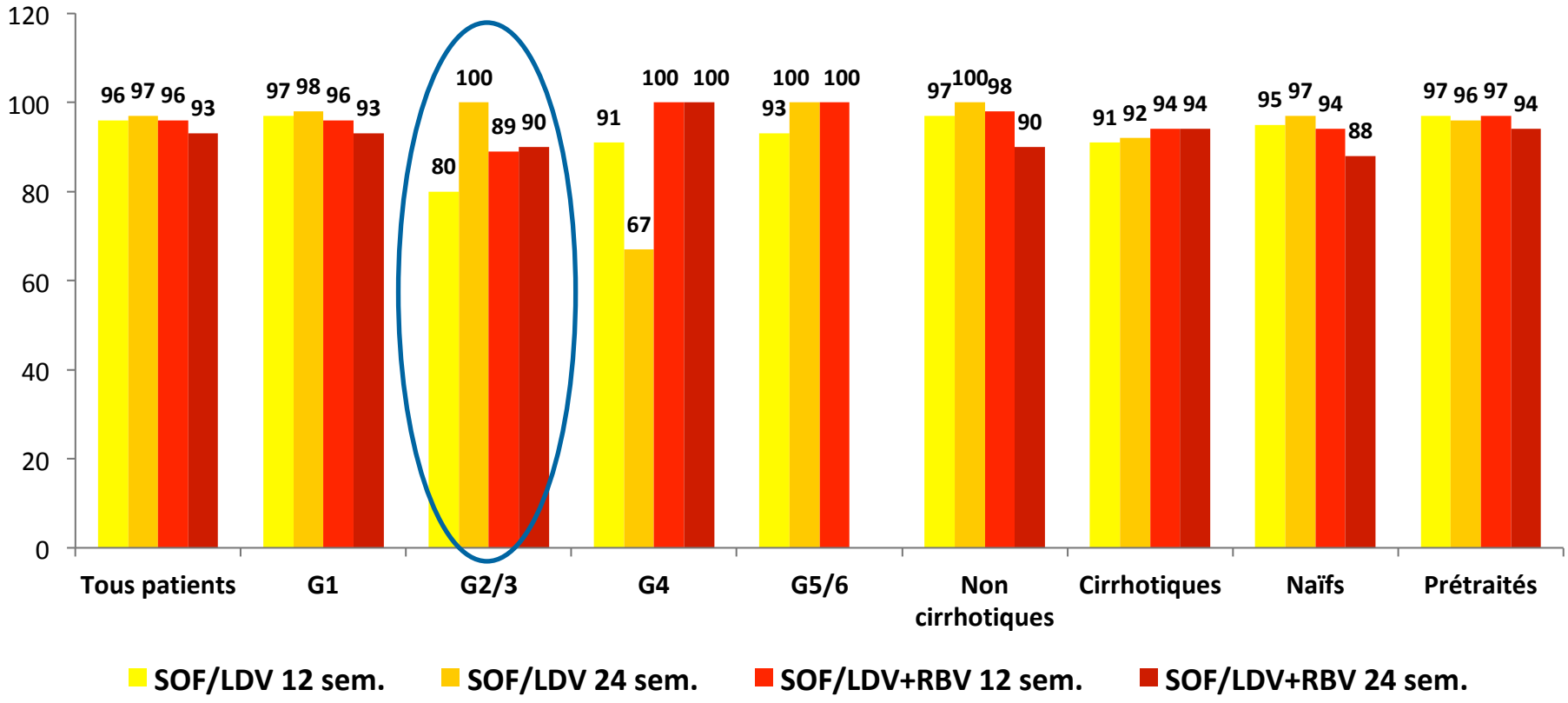
Adapted from Strader DB, et al. Hepatology 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2013. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2014. Jacobson I, et al. EASL 2013. Amsterdam. The Netherlands. Poster #1425. Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413. Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02; Afdhal N, et al. *N Engl J Med* 2014; 370: 1889-98; Kowdley K, et al. *N Engl J Med* 2014; 370: 1879-88.

Sofosbuvir/ledipasvir ± RBV



[1] *Mangia et al, EASL 2014,*
[2] *Afdhal et al, NEJM 2014*
[3] *Kowdley et al, NEJM 2014*

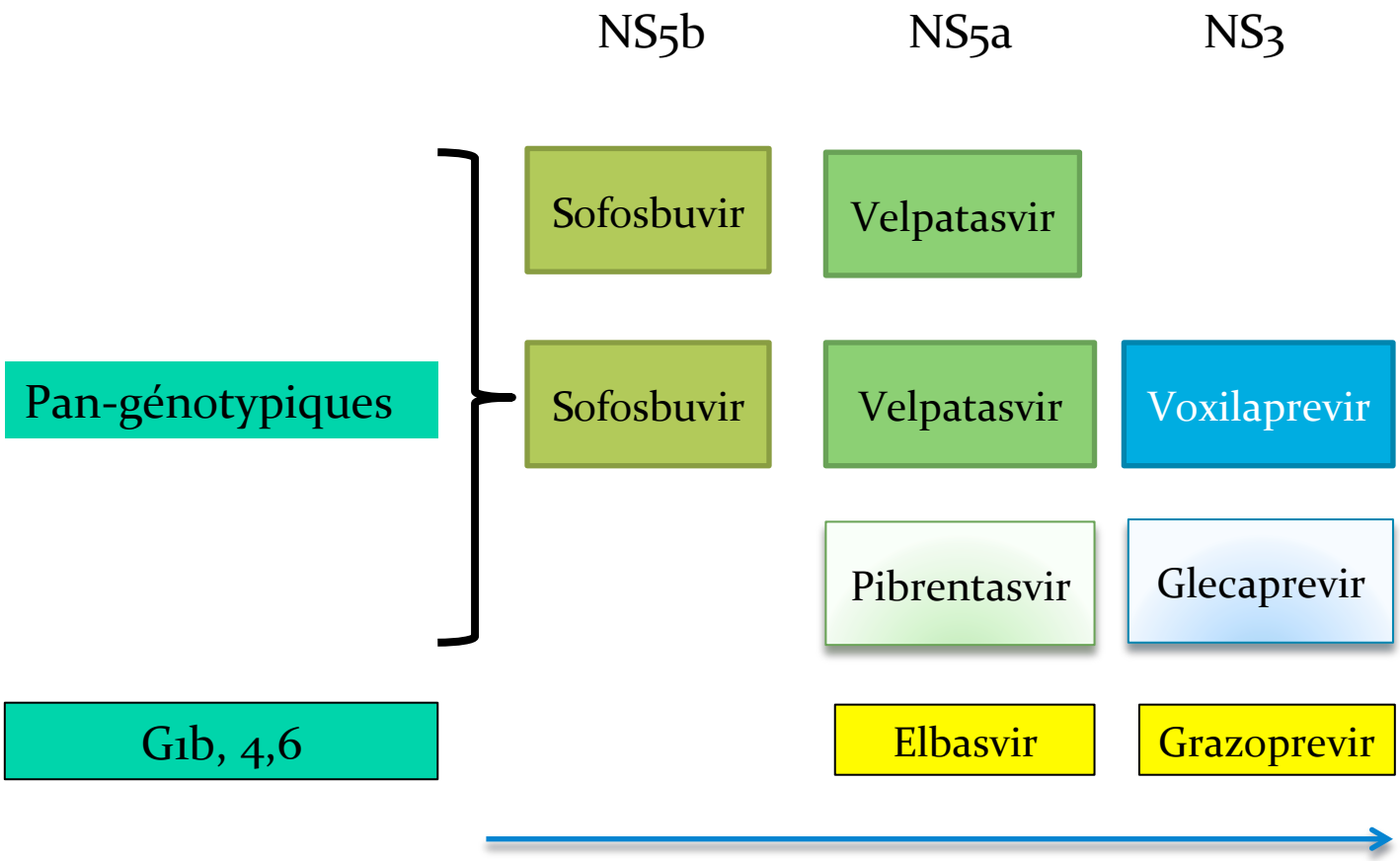
Sofosbuvir+Ledipasvir: Harvoni®



- 1 267 patients : 1 064 G1, 55 G2/3, 101 G4, 33 G5/6
- 358 avec RBV

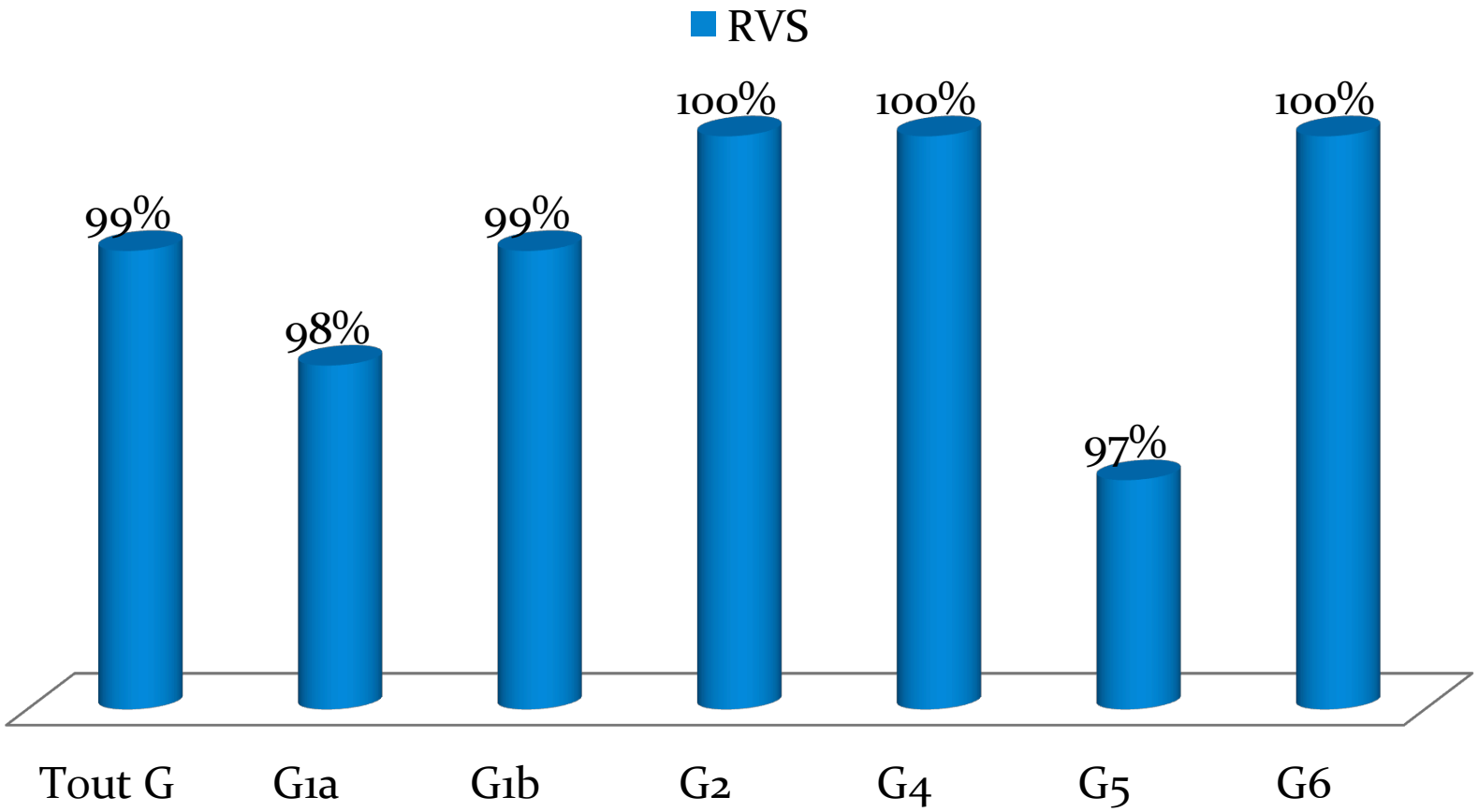
Pol S, Paris, AASLD 2017, Abs. 1087 actualisé

Les nouvelles options thérapeutiques



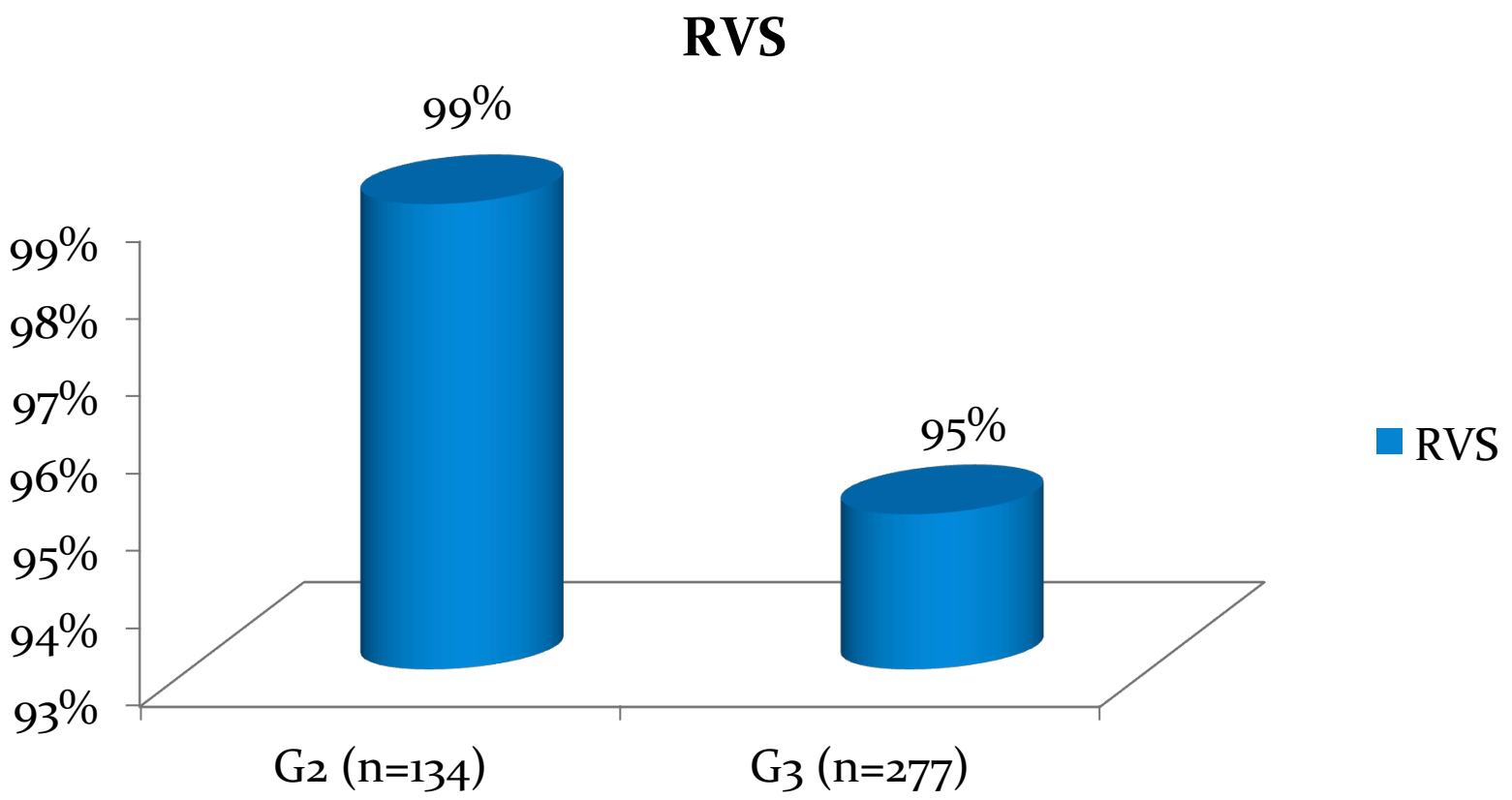
Durée : 8 à 16 semaines sans RBV

Sofosbuvir+Velpastasvir: Epclusa®
Génotypes 1,2,4,5,6



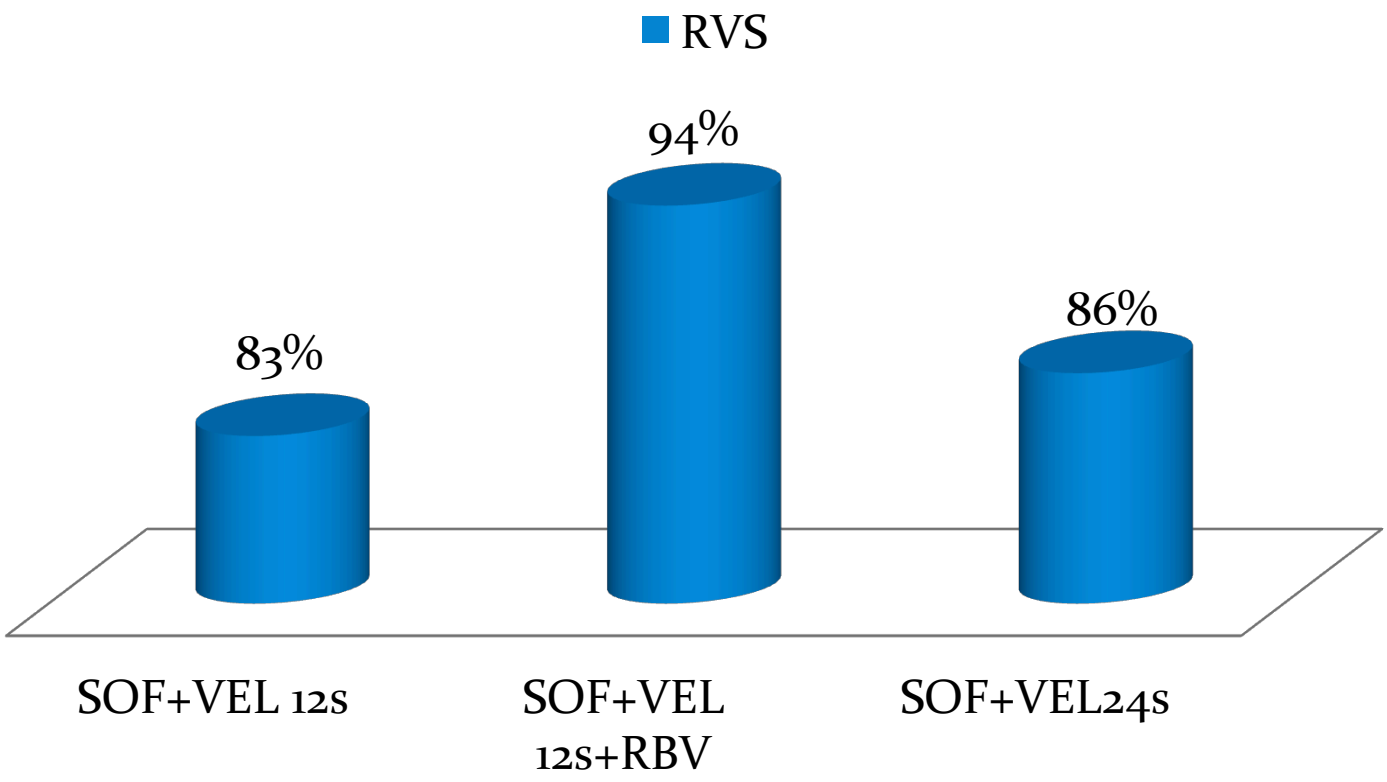
Feld et al, NEJM 2015

Sofosbuvir+Velpastasvir: Epclusa® Génotypes 2 et 3



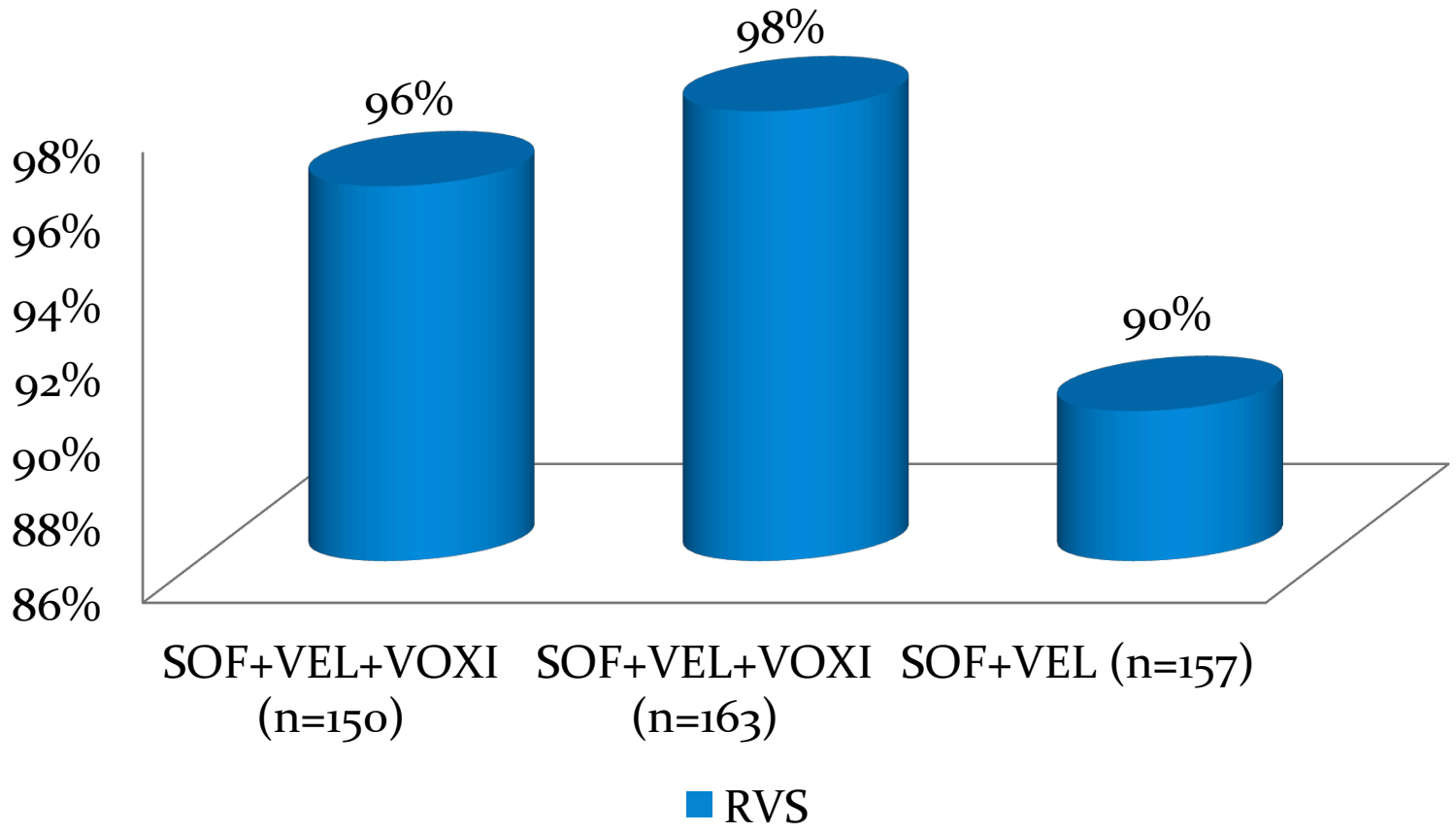
Foster et al, NEJM 2015

Sofosbuvir+Velpatasvir±Ribavirine
Cirrhose décompensée



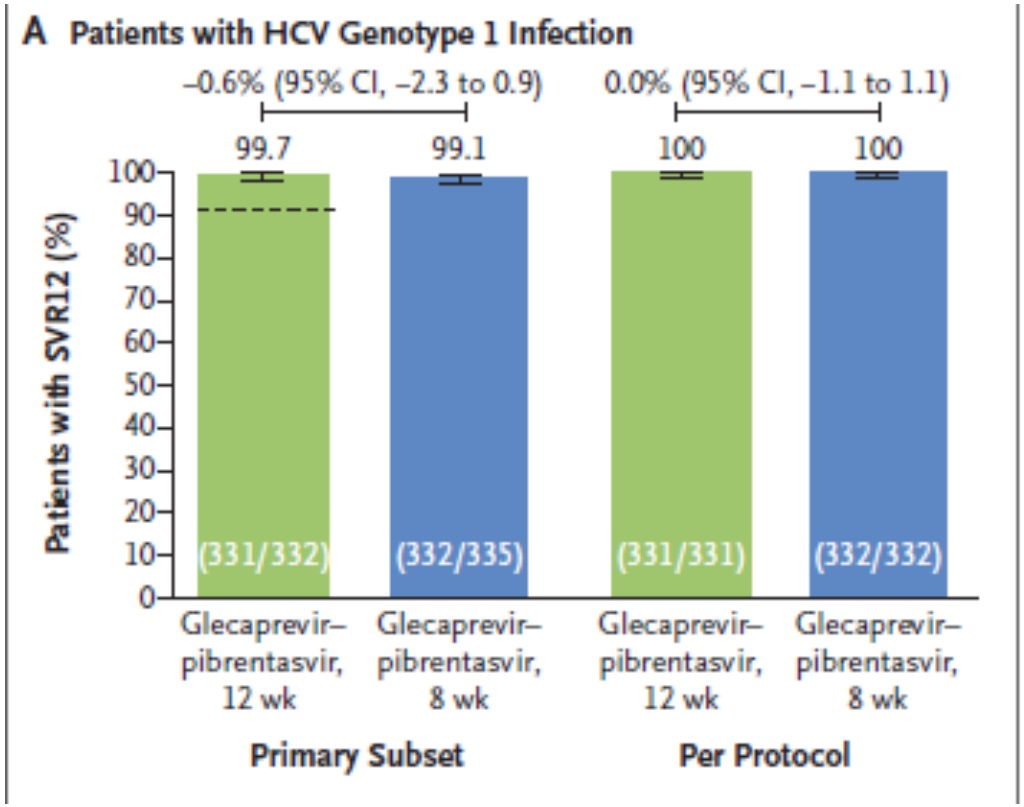
Curry et al, NEJM 2015

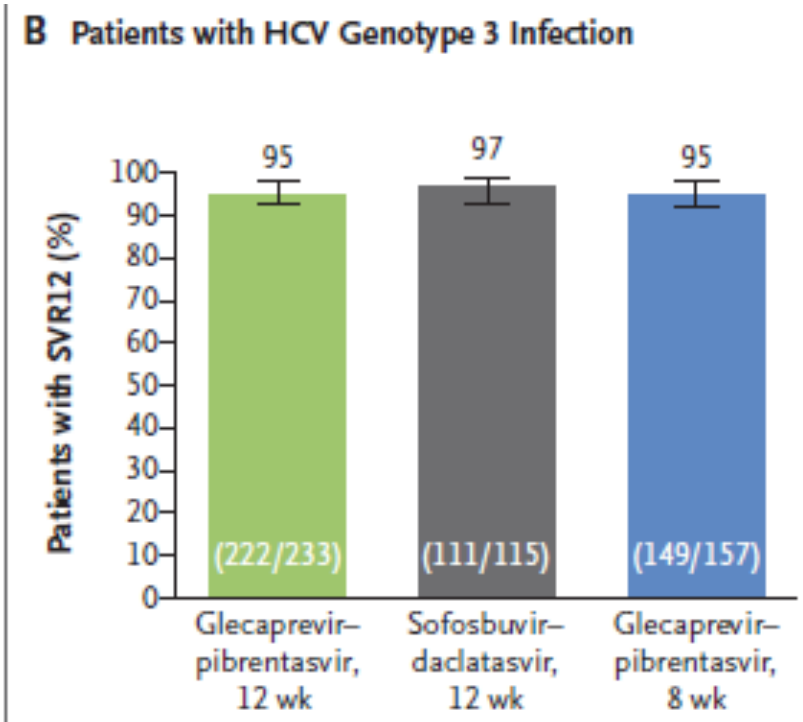
Sofosbuvir+Velpatasvir+Voxaliprevir: Vosevi® (en échec de DAA)



Bourlière et al, NEJM 2017

Glecaprevir+Pibrentasvir: Maviret®

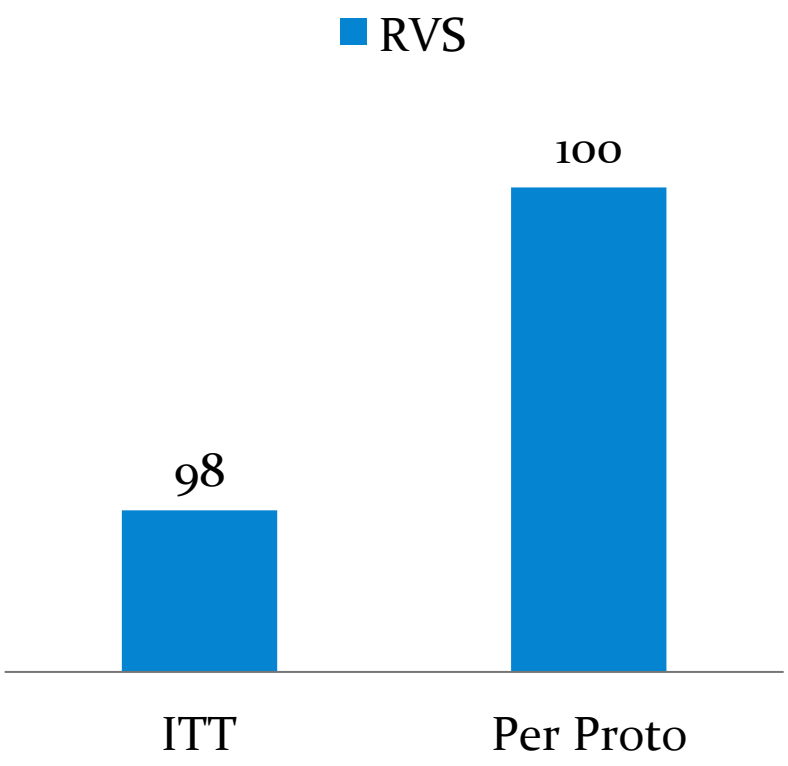




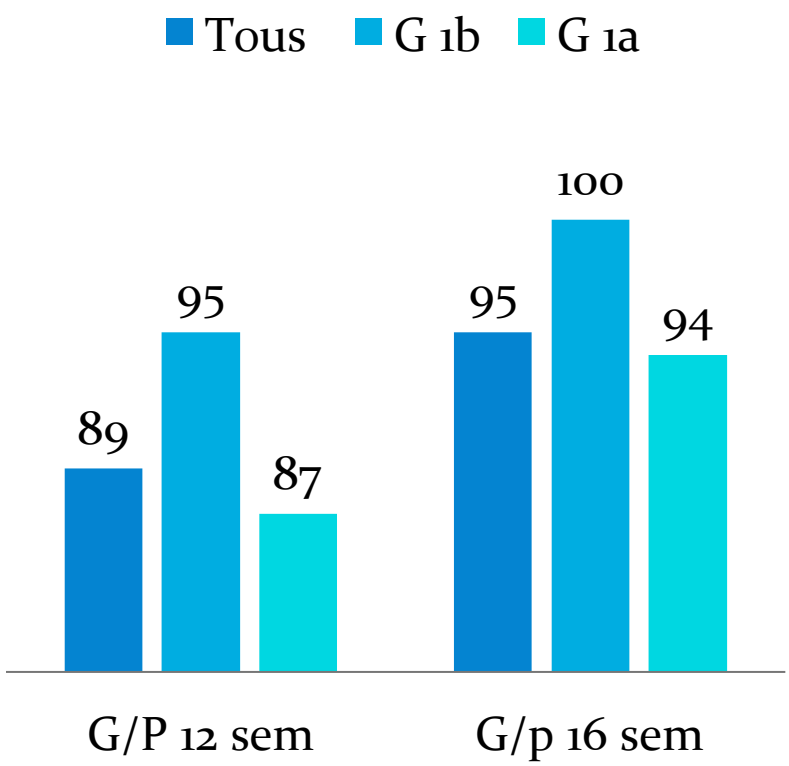
Zeuzem et al, NEJM 2018

G/P: Maviret®

Cirrhose (8 sem)

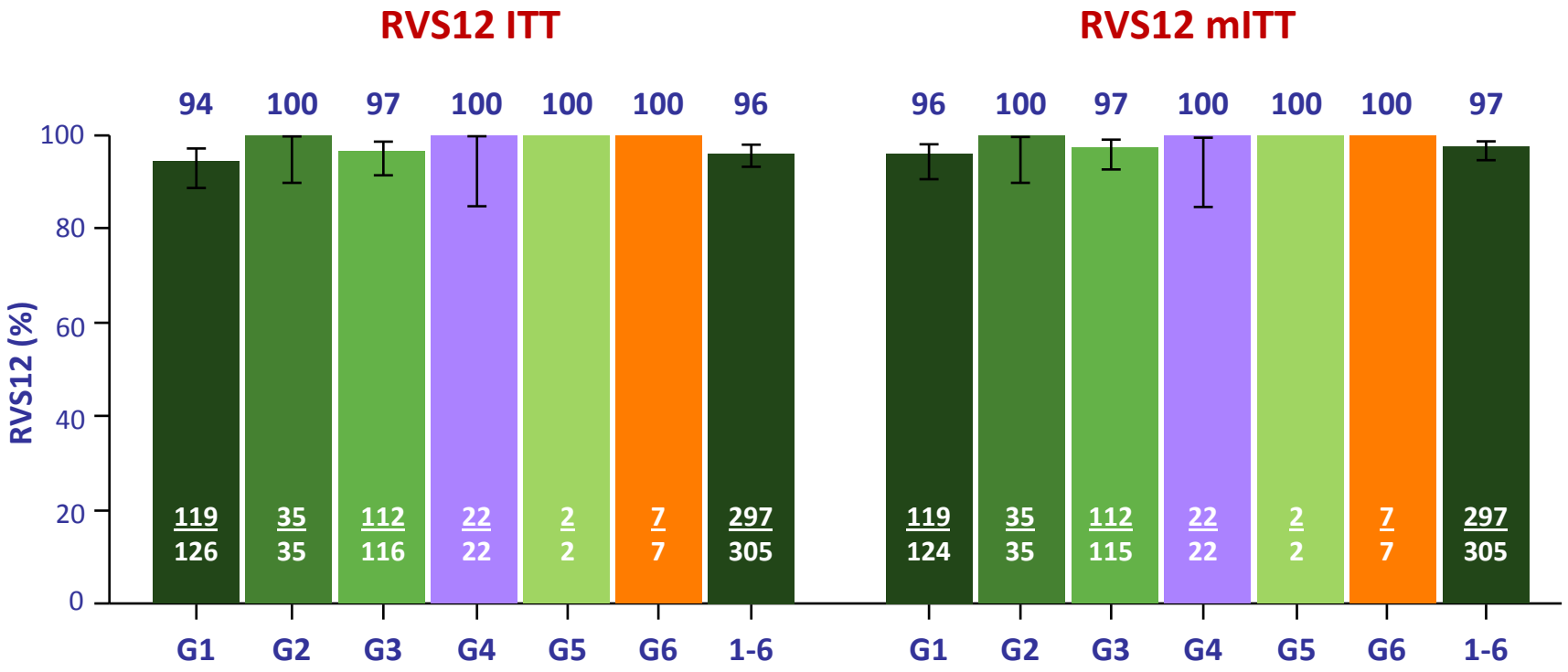


Non répondeurs NS5a±Sofosbuvir



Brown et a, AASLD 2018

Glecaprevir/Pibrentasvir des patients G1-6 ayant une cirrhose compensée

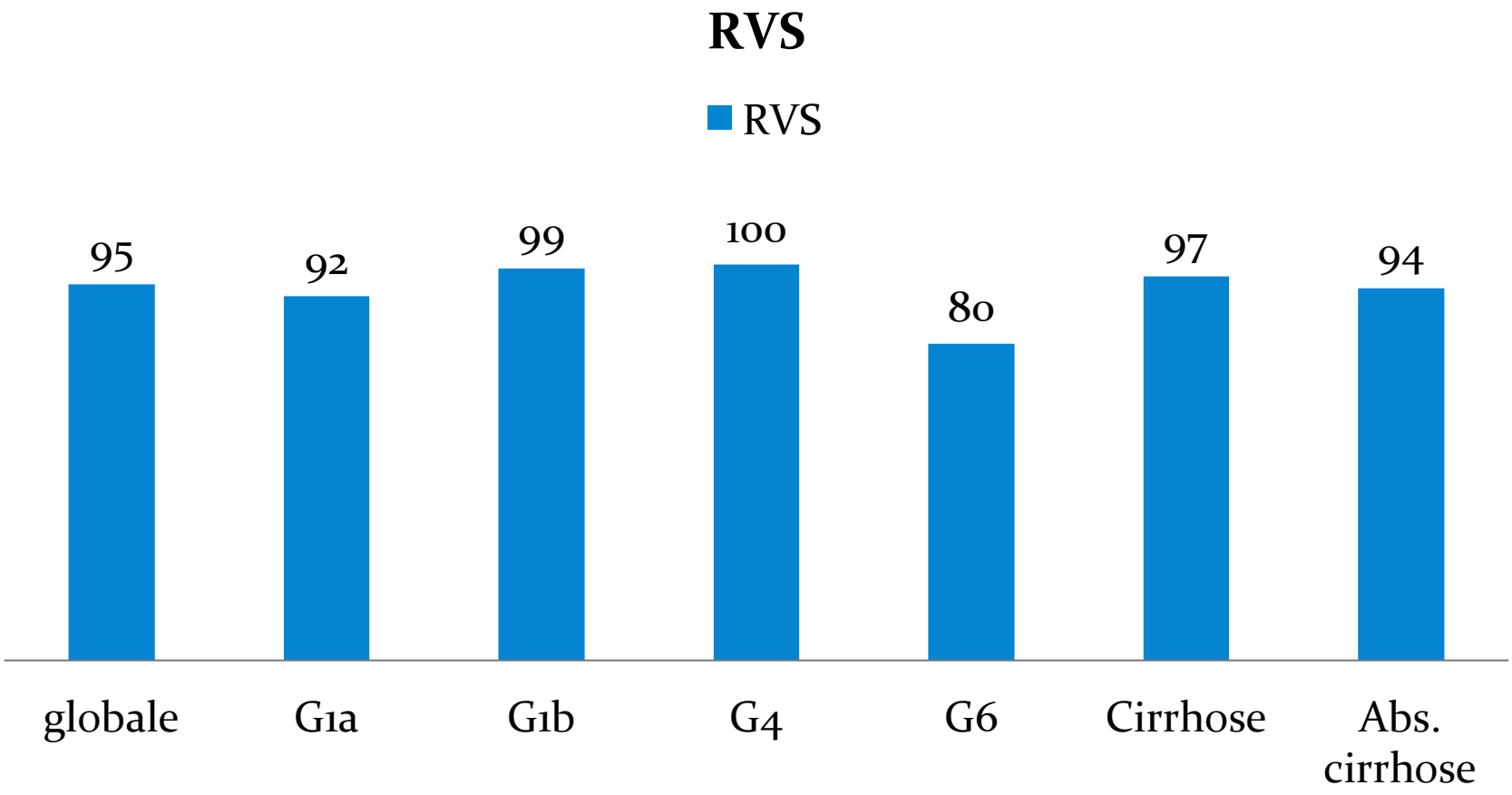


Raisons de non réponse, n (%)	n = 308
Echappement	5 (2)
Rechutes	3 (1)
Données manquantes	2 (< 1)
Arrêt	1 (< 1)

Raisons de non réponse, n (%)	
Echappement	5 (2)
Rechutes	3 (1)

Gane EJ, Nouvelle Zélande, AASLD 2017, Abs. 74 actualisé

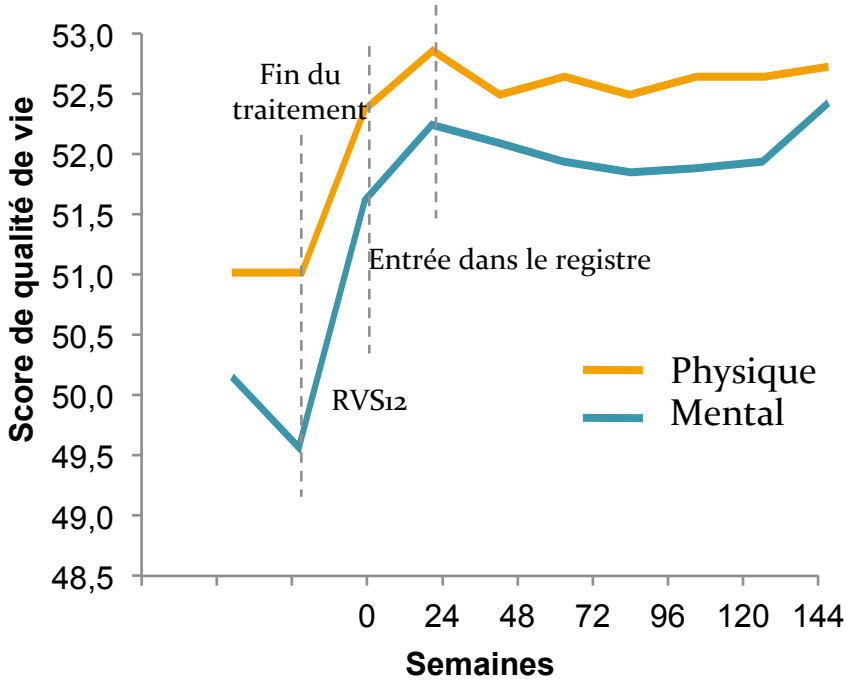
Grazoprevir/Elbasvir
Génotype 1b, 4, 6



Zeuzem et al, Ann Intern Med 2015

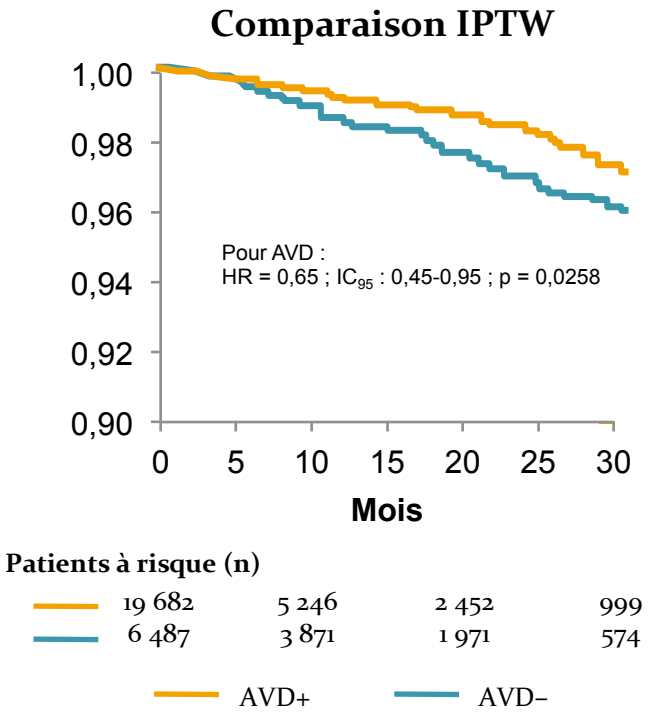
Un traitement, pour quel bénéfice?

3 486 patients traités à base de SOF



Qualité de vie

7 036 traités AVD



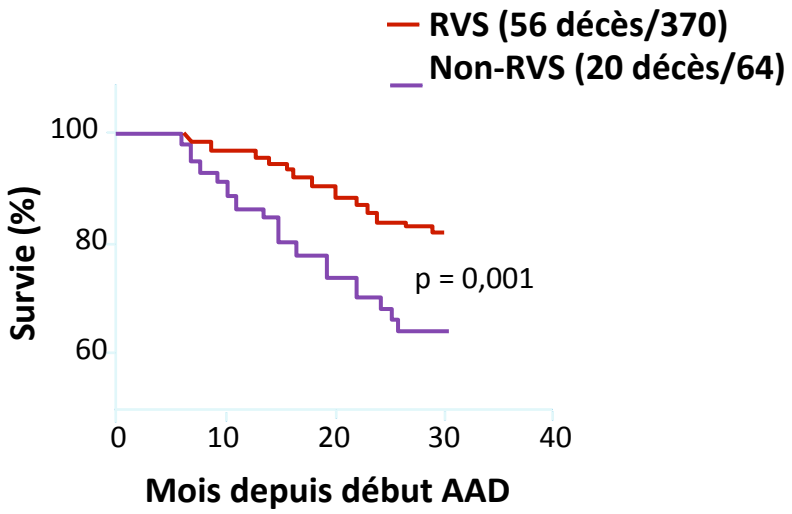
Survie

AASLD 2017 - D'après Younossi ZM et al., abstr. 64, actualisé,
AASLD 2017 - D'après Carrat F et al., abstr. LB28, actualisé

Cirrhose décompensée liée au VHC : quel est le bénéfice du traitement antiviral ?

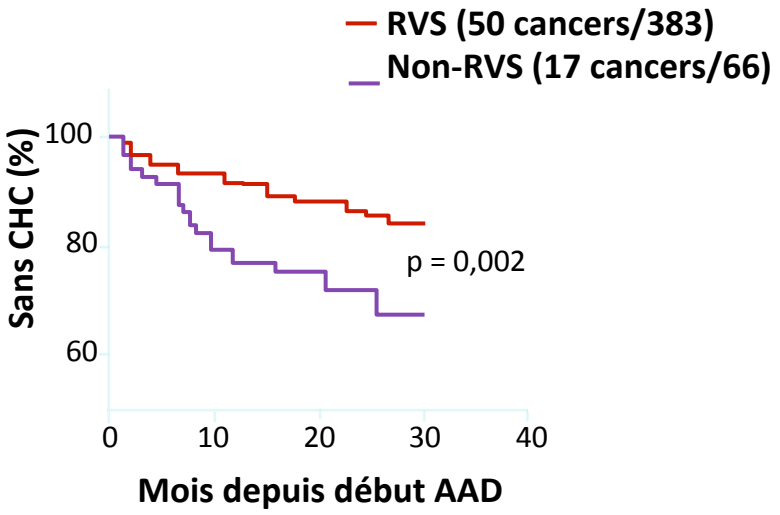
- 454 patients cirrhotiques avec ATCD décompensation et/ou Child B
- Traités par AAD 12 sem. ou retraités 24 sem. : 383 RVS+, 66 RVS-, 5 perdus de vue

Survie sans transplantation



Hazard ratio 0,44 (IC 95 % : 0,23-0,84)

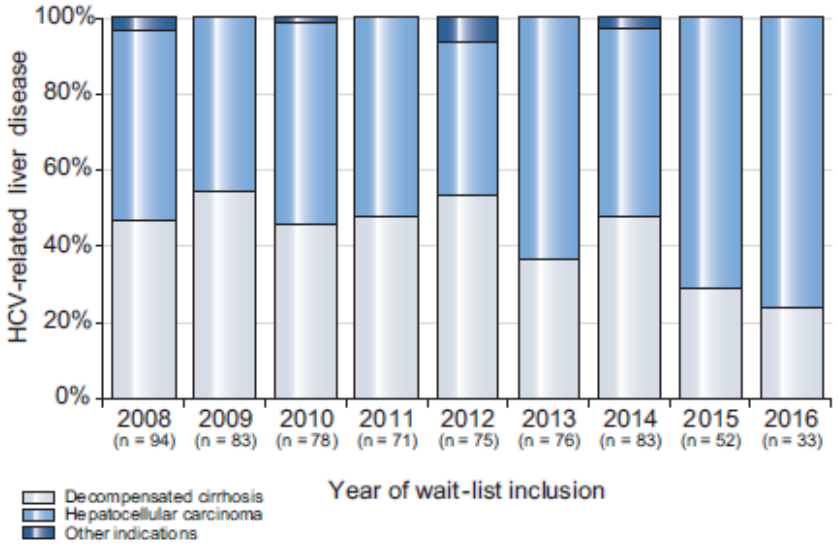
CHC de novo

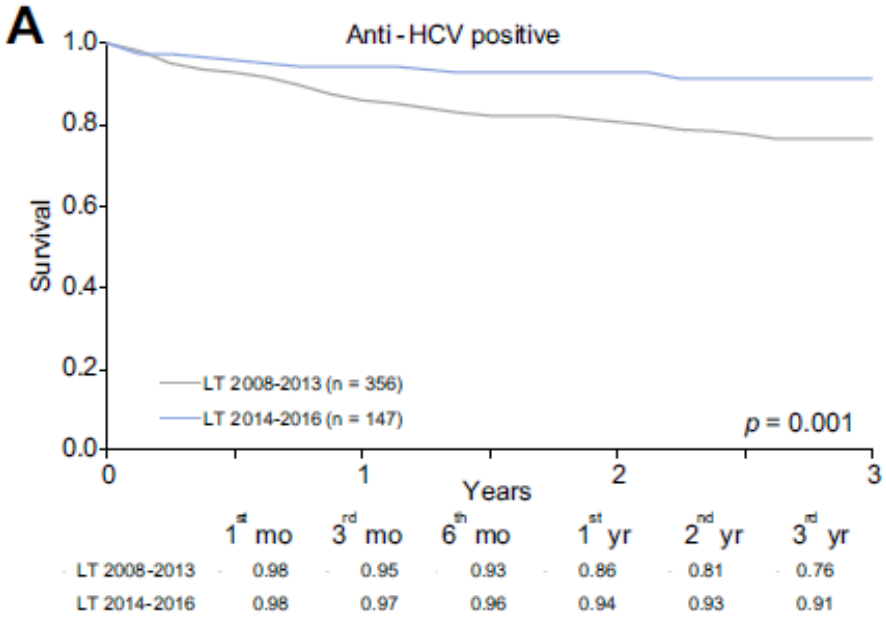


Hazard ratio 0,42 (IC 95 % : 0,21-0,88)

Cheung MCM, Royaume-Uni, EASL 2018, Abs. LBP-009 actualisé

En Transplantation





1484 patients
% en liste d'attente VHC: 47 à 35%

Crespo et al, J Hepatol 2018

Traitement de 1ère intention

- **2 options thérapeutiques** pan-génotypiques:
  - Epclusa®: Sofosbuvir+Velpatasvir: 12 semaines
  - Maviret®: Glecaprevir+Pibrentasvir: 8 semaines

- **Evaluer** les interactions médicamenteuses

- **RVS**: 12 semaines après la fin du traitement

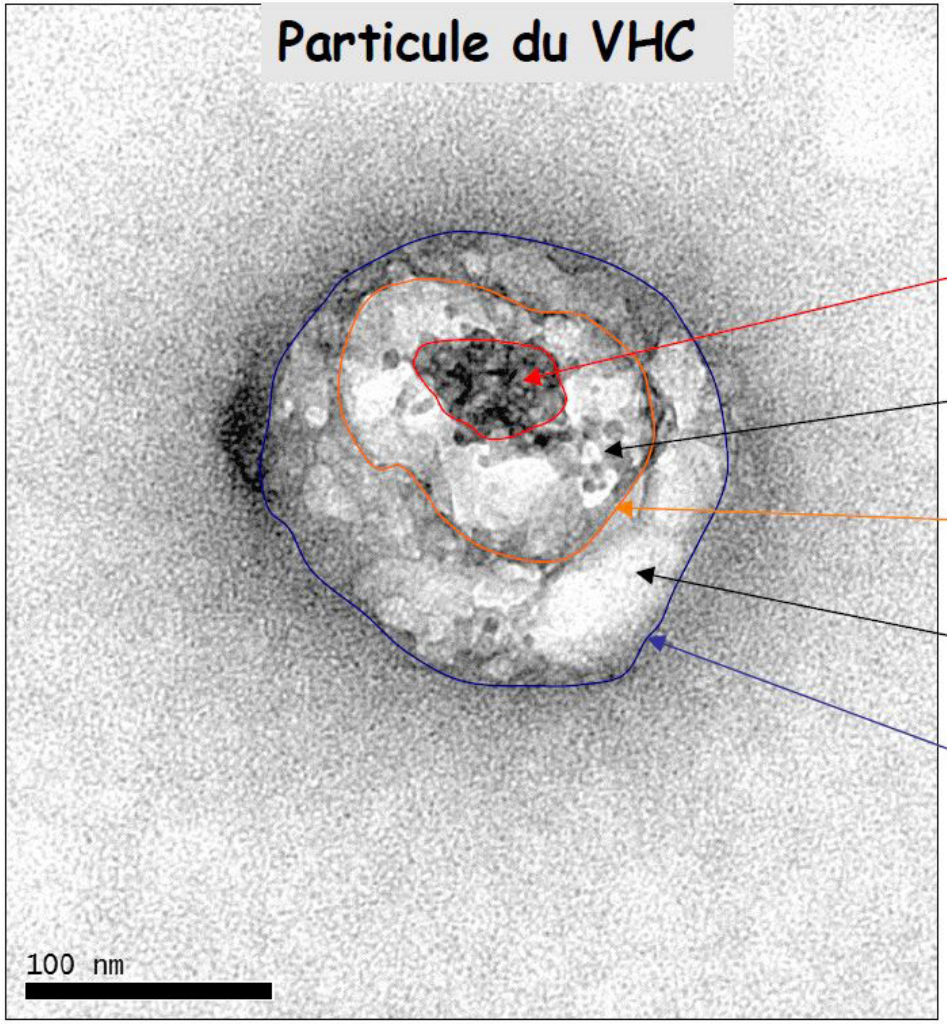
En cas d’échec

- **Vosevi®**: Sofosbuvir+ Velpatasvir+ Voxilaprevir: 12 semaines
- **Vosevi®± Ribavirine**: 12-24 semaines, Cirrhose G3
- **Epclusa®+ Ribavirine**: 24 semaines si cirrhose décompensée

Attention aux interactions médicamenteuses

	SOF/VEL	SOF/VEL/VOX	GLE/PIB
Antirétroviraux	+	+	+
Cannabis/cocaine	+	+	+
Statines	-	-	-
Antidépresseurs	-	-	-
Antipsychotiques	-	-	-
Amiodarone	Non	Non	Possible
Béta-bloquants	+	+	+ (sauf carvedilol)
Calcium-bloquants	-	Diltiazem	Diltiazem
Antihypertenseurs	+	+	+
Immunosuppresseurs	-	-	Ciclo et TDF
Antiagrégants plaq.	-	-	-
Anticoagulants	+	+	+

Le VHC, enfin sous le microscope



Contenu de la nucléocapside
= ARN viral

Nucléocapside
= Assemblage de protéines Core

Limite de la Nucléocapside
= Monocouche de phospholipides 2

Lipides
= Cholestérol, Triglycérides

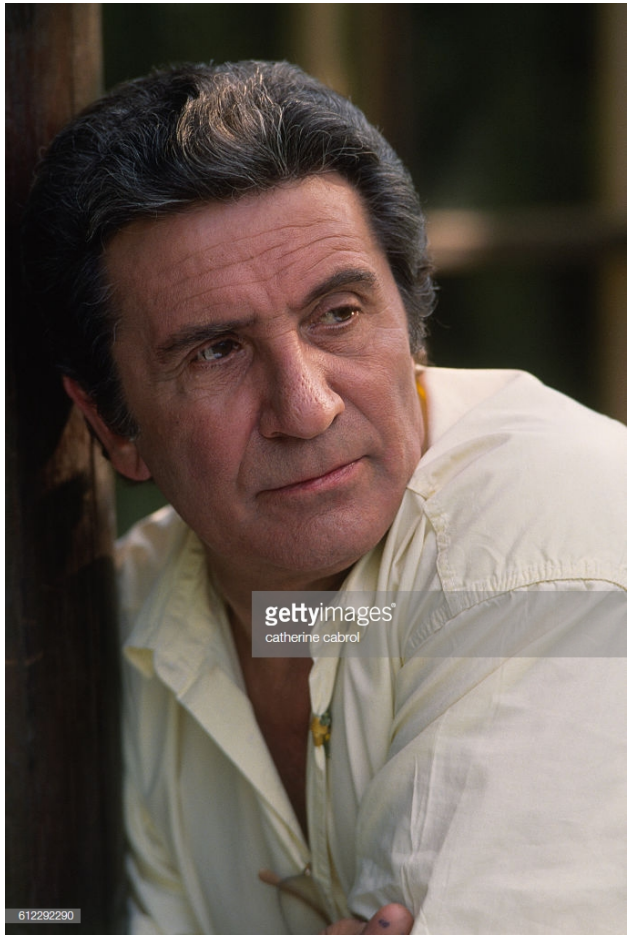
Enveloppe extérieure
= Monocouche de phospholipides 1

100 nm = 100 nanomètres

Piver et al, Gut 2016

Et maintenant

- Comme tout le monde est éradiqué par le traitement
- **Il faut**:
  - **Dépister** tout le monde
  - **Evaluer la fi**brose (marqueurs non-invasifs)
  - **Surveiller** les patients F3-F4
- **Les réserves** sont:
  - Dans les CSAPA, CARUD, Prisons, etc…
  - Les anciens patients non guéris qui ont oublié



Merci

- **Médecins:**
  - V Leroy, MN Hilleret, T Decaens, B Froissart, J Nana, A Keita, L Bouarioua
- **IDE** d'éducation thérapeutique et de pratique avancée
- **ARCs** (A Plagès, L Bordy)
- **Patients**